VOL. CLXXVIII, No. 3 SEPTEMBER, 1929 No. 690

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

FATAL INFECTION OF THE INTESTINES WITH BACILLUS AËROGENES CAPSULATUS. By JOSEPH SAILER, M.D., GEORGE M. LAWS, M.D., and JOHN EIMAN, M.D. . . 309

MONGOLIAN IDIOCY: THE MANNER OF ITS INHERITANCE. By MADGE THURLOW MACKLIN, B.A., M.D. 315

ASTHMA DUE TO THE MAYFLY. By KARL D. FIGLEY, M.D. 338

A CLINICOPHYSIOLOGIC STUDY OF THE PATHWAY OF PAIN IMPULSES IN CARDIAC DISEASE. By GEORGE I. SWETLOW, M.D., F.A.C.P. 345

CLINICAL AND ROENTGEN RAY FINDINGS IN THE STUDY OF THE HEART AND THE GREAT VESSELS. STUDY OF 100 CASES FROM THE CARDIAC CLINICS OF THE PHILADELPHIA GENERAL HOSPITAL. By GERTRUDE JACKSON CHANDLEE, M.D., and E. BURVILL-HOLMES, M.D. 364

THE EFFECT OF AMYTAL ANESTHESIA UPON THE UTERUS AND ITS USE IN OBSTETRICS. By D. L. DRABKIN, M.D., I. S. RAVDIN, M.D., J. C. HIRST, M.D., and M. E. LAPHAM, M.D. 379

OBSERVATIONS ON CORONARY THROMBOSIS. WITH A REPORT OF THREE RECOVERED CASES. By A. CARLTON ERNSTENE, M.D. 383

THE THERAPEUTIC INDICATIONS AND THE DANGERS OF THE INTRAVENOUS ADMINISTRATION OF SODIUM-PHENYL-ETHYL BARBITURATE (SODIUM LUMINAL) AND OTHER BARBITURIC ACID DERIVATIVES. By SOMA WEISS, M.D. 390

AN INTRATRACHEAL METHOD FOR PROLONGED ARTIFICIAL RESPIRATION. By LEOPOLD BRAHDY, M.D., and M. BERNARD BRAHDY, M.D. 405

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 42

Contents continued on page x

OWNERS AND PUBLISHERS
LEA & FEBIGER
PHILADELPHIA

COPYRIGHT, 1929, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

ACÉTYLCHOLINE

A New and Powerful Vasodilator*

Indicated for Arterial Spasms, Raynaud's Disease, Endarteritis Obliterans, Trophic Disturbances and Vagal Insufficiency.

*Available for Clinical Use as ACÉCOLINE

Manufactured by
LABORATORIES CHEVRETIN-LEMATTE
52 Rue La Bruyere, Paris

Sole Distributors for ACÉCOLINE in the United States

Anglo-French Drug Co. (U. S. A.), Inc.
1270 Broadway
New York, N. Y.

Anglo-French Drug Co. (U.S.A.), Inc.
1270 Broadway, New York, N. Y.

GENTLEMEN:—Without obligation on my part, you may send your booklet and samples of Acécoline.

..... M.D.

.....

..... C

Exch.
N.Y. Acad of Medicine
3-15-31

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1929

ORIGINAL ARTICLES.

FATAL INFECTION OF THE INTESTINES WITH BACILLUS AËROGENES CAPSULATUS.*

By Joseph Sailer, M.D.,

LATE CHIEF OF MEDICAL SERVICE, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

George M. Laws, M.D.,

ASSOCIATE GYNECOLOGIST, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

AND

John Eiman, M.D.,

PATHOLOGIST, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

This patient apparently had an infection of the intestinal tract with the Bacillus aërogenes capsulatus, causing an acute toxemia, from which she died. We have been unable to discover the record of any similar case, and the report seems justified, not only because the case may be unique at this time, but also because it may be possible to draw inferences regarding the nature of some intestinal infections with this organism.

Case Reports. S. F., a white female, aged twenty-five years, was admitted on the service of Dr. George M. Laws to the private floor of the Presbyterian Hospital, January 20, 1926. She had soreness in the right lower quadrant of the abdomen for five months, and had lost weight progressively. Her mother had died of kidney disease, following an operation (appendectomy); a sister was insane; another sister and her father were well. The previous history included measles, chickenpox and influenza, numerous sore throats and some abscesses of the ears. Menstruation had

* This was the last scientific paper prepared by Dr. Sailer, who died December 31, 1928.

been normal. She had noted tenderness in the right lower quadrant for several months, pain in the right sacral region and right hip at irregular intervals, and attacks of pain in the right lower quadrant, ascribed to gas. Micturition was normal; the appetite fair or poor; and there was chronic constipation, with the laxative habit, usually cascara. She thought that she was nervous. She had weighed 104 pounds during the summer of 1925. When admitted she weighed 93 pounds.

She was a thin, excitable young woman. The pupils were rather wide, but otherwise the head was normal. The heart and lungs were normal; the intercostal angle was acute, but the abdomen was otherwise normal; in particular no tenderness was elicited, and no masses were felt; but visceroptosis was suspected. The urine contained glucose, confirmed by the phenylhydrazin test, but the blood sugar was only 89 mg. per 100 cc. of blood. The clinical diagnosis was chronic appendicitis.

The operation was performed by Dr. Laws, assisted by Dr. Howell, the day after the patient's admission. The appendix was distended and crepitated on palpation, and the walls were congested. There were no adhesions, and no peritoneal exudate. The stump was inverted, and the wound closed without drainage. It was noted that the pelvic organs were normal, and that the appendix contained old hemorrhagic fluid. The following day the patient seemed well; there had been only a slight nausea and vomiting; but on the morning of the 23d a scarlatinal rash was noted, involving the face, neck, shoulders and upper thorax. The temperature was normal. She hiccoughed all day, and she vomited occasionally. The abdomen was flat and soft. The throat was not sore. The patient was apathetic, but seemed concerned about the outcome. The morning of the 24th the erythema was deeper and more extensive; the throat was sore, and although the temperature was still normal, the skin was hot and dry. An enema was given, and was followed by the expulsion of a greenish fluid with an intensely offensive odor. She also had some diarrhea, and the movements had the same offensive odor. The patient was weak, the pulse rapid and almost imperceptible. At 2.50 P.M. the blood pressure was 48 systolic; the diastolic pressure was not obtainable. The blood was counted and reported 4,250,000 red cells and 23,650 white cells.

At this time I first saw the patient. She lay in bed, the picture of exhaustion, obviously very weak, but conscious. The rash had nearly faded, although there were some traces of it still on the upper chest. The heart-sounds were clear, but weak; some râles of edema were heard in the lungs; the abdomen was flat, soft, not tender, and peristalsis was rather active. The reflexes were normal.

The condition was puzzling. There was no lack of signs, but it was difficult to interpret them. The following points were considered:

1. The profound prostration of the patient, with the weak, rapid pulse.
2. The erythematous rash.
3. The afebrile leukocytosis.
4. The intensely foul odor of the intestinal discharges.
5. The hypotension.
6. The previous history of the case.

Obviously the condition resembled some of the manifestations ascribed to toxins, although in most of these the supposed toxin is rarely, if ever, found. The profound prostration, the expression of

utter weariness, reminded me strongly of the cases of gas-bacillus poisoning that I had seen during the World War. They also had the weak and rapid pulse.

The erythematous rash was never explained. No reference to it was found in literature, none of our dermatologic friends could help us, and it is simply an observation to record.

The afebrile leukocytosis was more helpful. I have observed this in chronic or subacute pancreatitis, and I recalled dimly that I had heard it mentioned as being found in gas-bacillus infection. It also occurs in leukemia, after splenectomy, in polycythemia, and sometimes in some of the forms of pseudoleukemia. All of these could be disregarded, and the entire absence of tenderness or abdominal signs rendered pancreatitis unlikely. It reinforced the earlier thought of gas-bacillus infection.

The intensely foul odor of the intestinal discharges was merely suggestive. As nothing is known of massive infection of the intestinal tract by the gas bacillus, there is no information regarding the nature of the discharges. It seemed plausible to assume that they might be offensive, but there was no certainty. At least the cadaveric odor of muscular tissue infected by this organism was not against the assumption that the feces might be disagreeable.

The hypotension at the time was not significant, but later, after consultation with Professor Richards of the University of Pennsylvania, we realized that it might have been considered the most significant feature. During the World War, Professor Richards had been assigned the problem of studying the physiologic effects of the toxins of various microörganisms that produced gas gangrene. This work, which could it have been completed would have been extremely valuable, was interrupted by the conclusion of the war. The only definite fact that had been ascertained was the extraordinary reduction of the blood pressure of dogs to whom the toxins had been administered. Professor Richards showed us his protocols, and it is his and our hope that this work can be resumed and extended later. At any rate, it seems conclusive that these toxins cause hypotension.

The previous history at that time was misleading. Dr. Laws and I could not ignore the recent operation, although it was not demonstrable later that it had any effect upon the course of the case, excepting as it may have lowered the patient's resistance. We concluded, however, that the most reasonable diagnosis was intestinal infection with the gas bacillus. It remained to devise some method to confirm this diagnosis. A cotton swab was therefore gently introduced into the rectum, and then smeared upon a glass slide. This was repeated several times, and the slides immediately taken to the laboratory and stained by Gram's method. The picture obtained was typical, showing large, deeply-staining bacilli almost covering the slide, and was compared with several textbook

illustrations that were similar, all apparently made from smears of cultures.

An effort was immediately made to obtain some of the antitoxic serum prepared by H. K. Mulford Company against the gas bacillus. This has been used effectively in many surgical cases of gas bacillus poisoning, and it offered the only chance to prolong the patient's life. It was Sunday afternoon; the Mulford laboratory was closed, and although one of the officials promised to send us some very early Monday morning, nothing better could be done. We tried other places, but there was no serum to be had. It was then 7 P.M.

The subsequent course of the case was as follows:

7.10 P.M. Pulmonary edema commencing.

7.27 P.M. Adrenalin hydrochlorid (1 to 1000) ♏ xx, atropin sulphate $\frac{1}{50}$ gr., hypodermatically.

7.28 P.M. Blood pressure, 52; pulse, 116.

7.33 P.M. Blood pressure, 60; pulse, 136.

7.38 P.M. Blood pressure, 50; pulse, 140.

7.43 P.M. Blood pressure, 38. No pulmonary edema. At this time the patient was cyanosed and an attempt was made to do a venesection. This was probably inadvisable, but as the blood would not flow through the cannula, nothing was accomplished.

7.44 P.M. Adrenalin hydrochlorid, ♏ xx was given hypodermatically.

8.12 P.M. Blood pressure, 30.

8.15 P.M. Blood pressure, 30.

8.17 P.M. Adrenalin, ♏ xx.

8.20 P.M. Blood pressure, 30 (?).

8.25 P.M. Pulse, 140.

8.26 P.M. Blood pressure, 26.

8.34 P.M. Adrenalin, ♏ xx.

8.35 P.M. Blood pressure (?).

8.52 P.M. Blood pressure (?); pulse, 160.

9.25 P.M. Death.

Atropin relieved the pulmonary edema. The adrenalin would have been given intravenously, but the veins were collapsed. An electrocardiogram was taken Sunday afternoon. It showed rapidity of the pulse, poor electromotive force, regular rhythm, normal conduction time, and a suggestion of muscular failure. Permission was granted for an autopsy which was performed one hour and twenty minutes after death.

Autopsy. Subject is an adult white female, weighing about 85 pounds, and measuring 59½ inches. Nutrition is fair, musculature fair. Postmortem rigidity is very slight but generalized. Finger nails of the right hand are purplish. Skin is dry and shows no jaundice. There are no scars, edema, abrasions or generalized adenopathy. There is a recent incision over McBurney's point, measuring 4.5 cm. It is closed with a subcuticular stitch; it is clean and is healing by primary intention. Both hands show complete syndactylism of the third and fourth fingers.

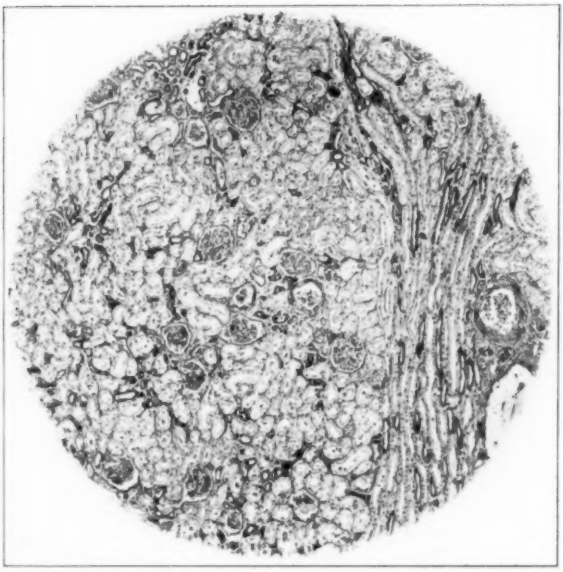


FIG. 1.—Low power of kidney, magnification 57 diameters.

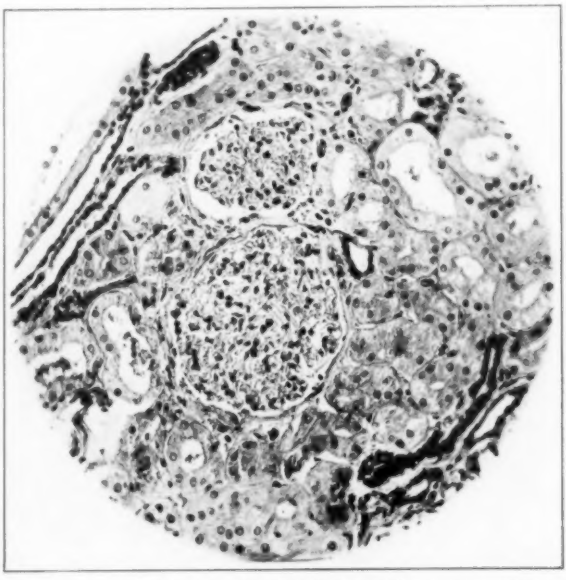


FIG. 2.—High power of kidney, magnification 230 diameters. The nuclei of cells lining capillaries of Bowman, capillaries are engorged, the spaces of Bowman contain small amounts of albuminous material and a few red cells. The nuclei of the cells lining the capsule of Bowman are swollen. The cells of convoluted tubules are swollen and granular. Lumina of tubules contain albuminous material.

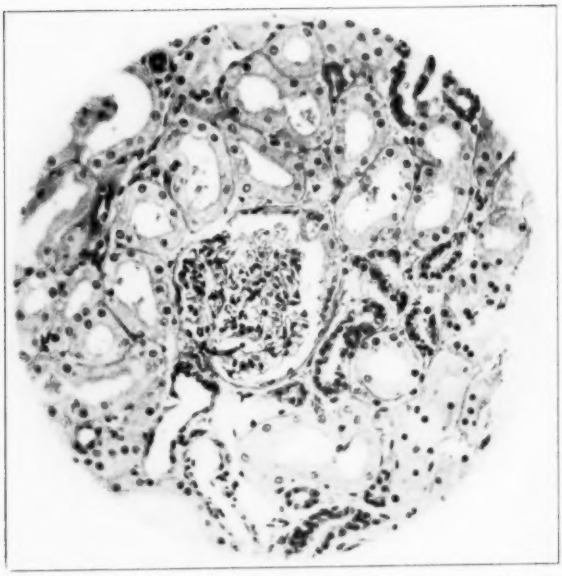


FIG. 3.—High power of kidney, magnification 230 diameters. Glomerulus shows necrosis of capillary loops.

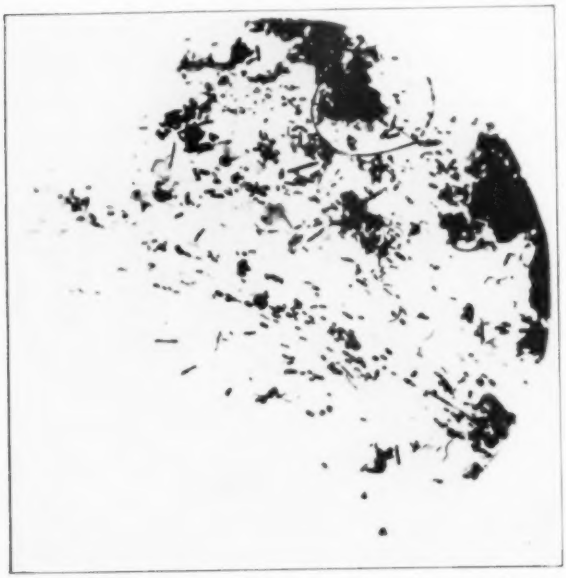


FIG. 4.—Smear from sticky mucus over ulcers in colon.

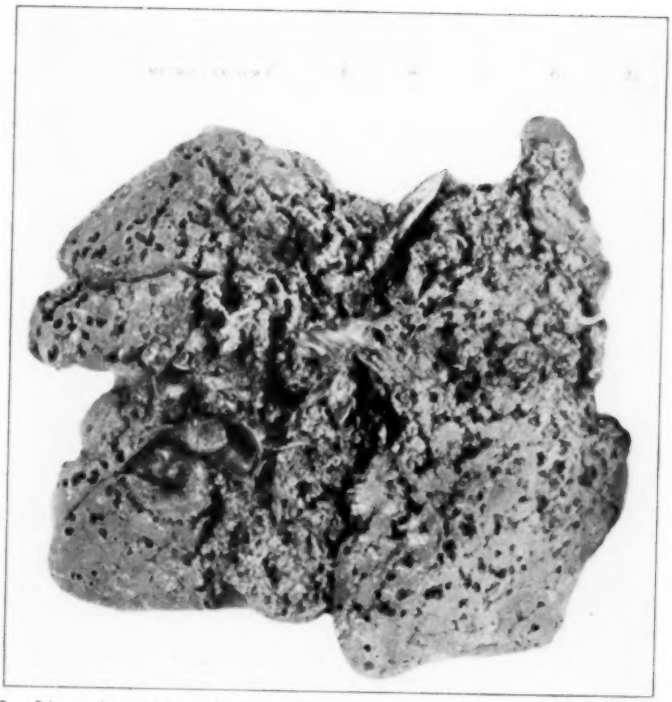


FIG. 5.—Liver of a rabbit six hours after injection of 2 cc. of twenty-four-hour culture of Bacillus welchii and incubation of 37° C.

Head. Shows no abnormalities in size or shape. *Ears and nose;* no external lesions. *Eyes:* Conjunctivæ pale, pupils smooth, round and equal, 7 mm. in diameter. *Mouth:* Mucous membranes are very pale. The teeth are in good condition.

The abdomen is flat, the wall is about 2 cm. in thickness.

Relations of Abdominal Viscera. Height of diaphragm: Right side, third interspace; left side, fourth interspace. Liver is 2 cm. below the costal margin in the right midclavicular line. The omentum is rather thin and is spread over the small intestines. The peritoneum is pale, smooth and glistening and contains no excessive fluid. Intestines are uniformly but slightly distended with gas; their peritoneal covering is pale, smooth and glistening. The appendix has been removed, and the stump has been inverted. The cecum at the point of inversion of the stump of the appendix is clean and does not show even small amounts of exudate or fibrin. There is no leakage. The cecum is mobile. There are several firm bands of adhesions between the lower surface of the right lobe of the liver, and the splenic flexure of the colon and the first and second portions of the duodenum. The foramen of Winslow is occluded by dense fibrous adhesions.

Thorax. Is long and narrow. Muscles are red in color and fairly well developed. They appear to contain more blood than usually seen. The pleural cavities are negative. The pericardium is negative.

Heart. Extends 1.7 cm. to the right of the midline and 6.5 cm. to the left of the midline. There are no thrombi in the pulmonary arteries. The heart weighs 170 gm. and measures 11 by 7.5 by 4.5 cm. The blood is liquid in the large vessels, but coagulated in a few minutes after being placed in a test tube. No evidence of thrombosis of the coronary vessels. Heart is contracted. The orifices and leaflets show no noteworthy lesions. Foramen ovale is occluded. Myocardium is fairly firm in consistency and brownish-red in color.

Lungs. Show slight passive congestion at the bases. No infarcts or other noteworthy lesions.

Spleen. No noteworthy lesions.

Uterus and Adnexa. No noteworthy lesions.

Liver. Weighs 1080 gm. Measures 25.5 by 22 by 7 cm. Edges sharp. Consistency, flabby. Section yellowish to brownish. Appearance cloudy; liver lobules indistinct. Amount of blood about normal.

Gall Bladder. Dense bands of adhesions around the neck of the gall bladder. Wall slightly but uniformly thickened. Contains thin, dark bile. Hepatic, cystic and common ducts are patulous.

Pancreas. Weighs 55 gm., measures 14 by 3.2 by 4.2 cm. Somewhat flabby in consistency. Lobules are distinct.

There is no evidence of thrombosis or other pathologic changes in the portal and mesenteric vessels. The mesenteric lymph nodes are moderately enlarged, the largest measuring 1 by 0.8 cm. The retroperitoneal lymph nodes are also moderately enlarged. The capsules of these nodes are rather tense and they are pale purplish-gray in color.

Esophagus. Negative.

Stomach. Negative, except for slight congestion at the cardiac end.

Duodenum and Jejunum. Negative.

In the upper part of the ileum are seen transversely running hemorrhagic lines; approaching the cecum they become wider so that at a point 100 cm. above the ileocecal valve hemorrhagic bands merge, and the mucosa assumes uniformly hemorrhagic appearance. The solitary lymphoid follicles are slightly enlarged but the Peyer's patches do not stand out prominently.

Large Intestine. The mucosa has a brownish to pearly-gray, opaque appearance. The cecum shows very numerous irregular confluent

superficial ulcers. The base of the ulcers rests on the submucous coat. In the ulcerated areas are seen slightly enlarged lymphoid follicles. The upper part of the ascending, transverse and descending colons are free from ulcers. The sigmoid shows numerous ulcers similar to those seen in the cecum. The stump of the appendix projects into the lumen of the cecum for 1 cm. The stump is occluded and there are no evidences of infection or leakage. Over the lower part of the ileum and in the colon are seen moderate amounts of thick, sticky grayish mucus, which is rather tenaciously adherent to the mucosa.

Adrenals. Show no gross lesions.

Left Kidney. Weighs 80 gm., measures 8.5 by 4.5 by 3 cm. It is fairly firm in consistency. Capsule strips easily and leaves a pale, smooth surface. Section surface does not bulge. Cortex, 7 mm. Medulla, 18 mm. Cortical striations fairly distinct. The cortex and medulla pale, pinkish to yellowish. The pyramids are purplish. The lining of the pelvis is pale, smooth and glistening.

Right Kidney. Weighs 75 gm. Similar to its fellow.

Ureters and Urinary Bladder. Negative.

Aorta. Negative. *Vena Cava* and branches. Negative. No gas seen in vessels anywhere.

Microscopic Examination. *Kidney:* The larger bloodvessels show no noteworthy changes. The cells lining the convoluted tubules are slightly granular and swollen; most of the lumina, however, remain open and contain albuminous material and partly broken-down red cells. The glomeruli appear to be rather cellular. The cellularity is due mainly to marked swelling of the nuclei, only here and there are seen dividing cells. The capillaries of the tufts are engorged, their lining endothelial cells are swollen. Only here and there is seen a necrotic loop. Only a few glomeruli show necrosis of several loops. The cells lining the capsule of Bowman are swollen in places, but there is no actual desquamation. The spaces of Bowman contain either albuminous material, red cells, or both. The collecting tubules show no noteworthy changes.

Microscopic Diagnosis.

Acute ulcerative ileo-colitis. Acute lymphadenitis of the mesenteric and retroperitoneal lymph nodes.

Early acute diffuse glomerulonephritis.

Cloudy swelling of the heart.

Toxic and fatty degeneration of the liver.

Spleen: Minor lesions.

Lungs: Slight passive congestion.

Pancreas: Minor lesions.

Adrenals: Marked hyperemia.

Blood removed from right side of the heart one and a half hours after death showed: 85 mg. per 100 cc. of blood urea nitrogen, and 640 mg. per 100 cc. of blood chlorids.

Culture from heart's blood: Negative.

Mucus from the lower part of ileum and colon shows very large numbers of Gram-positive bacilli, with blunt ends which morphologically resemble B. welchii. Some of this mucus was inoculated into tubes of brain bouillon. Gas was produced in a few hours. Some of the tubes were covered with a layer of paraffin oil; these tubes formed less gas. 2 cc. of a twenty-four-hour brain-bouillon culture were injected intravenously into a rabbit, and the animal was sacrificed ten minutes later. The rabbit was then placed in the incubator at 37° C. for six hours. The animal was tremendously distended with gas. There was crepitation in the interfascial spaces. The muscles were cloudy, friable, and had the appearance of having been boiled.

Characteristic odor of Bacillus welchii gas was noticed. The liver was studded with innumerable bubbles of gas and had a "foamy" appearance. Some of the bubbles had broken through the capsule. Bacillus welchii organisms were recovered on smear and culture from the heart's blood and liver. Subcultures were made in litmus milk. In twenty-four hours they showed much gas, acid reaction, coagulation, but the casein was not completely digested. At a later date spore formation was observed, which was more rapid in the paraffin-oil-covered tubes.

Cause of Death: Severe toxemia probably due to absorption of the Bacillus welchii toxin from the intestines.

Summary. Consideration of the clinical course and the findings of the autopsy lead us to adhere to the diagnosis of gas-bacillus infection. The changes in the kidney might, we believe, have escaped the attention of a less alert pathologist than Dr. Eiman, and moreover the lesion is too slight to be regarded as the cause of death. No other lesion was found that might be suspected, and indeed, if the Bacillus aërogenes capsulatus had not been found and cultured, the cause of death might have been unknown, even after the autopsy. The possibility of diabetes seems to have been definitely excluded. Apparently the most valuable signs of this condition are the profound prostration, the hypotension the afebrile leukocytosis, the peculiar fetic odor of the stools, perhaps the erythematous rash and the discovery of large Gram-positive bacilli with rounded ends in smears from the rectal contents.

MONGOLIAN IDIOCY: THE MANNER OF ITS INHERITANCE.

By Madge Thurlow Macklin, B.A., M.D.

(From Department of Anatomy, Medical School, University of Western Ontario, London, Ontario.)

Since Mongolian idiocy was first differentiated as a clinical entity by Down,[159] its etiology has been a matter of interest, inasmuch as it frequently appeared in families in which there was no neuropathic taint.

Theories of Etiology. Various theories have been advanced as explanations of its occurrence, the most favorably received being those to be mentioned. Perhaps most widely accepted was the one which attributed this deformity in the offspring to reproductive exhaustion on the part of the mother, since numerous observers stated that the Mongolian idiot was usually born after a long series of pregnancies. Occasionally however, the Mongol was born in the first or second pregnancy, so that here reproductive exhaustion could scarcely be considered as the cause. In some of these instances, the mother was found to be above the average age of primiparæ or

secundiparæ, so that emphasis was placed not upon the number of pregnancies, but upon the advanced age of the mother as the causative agent. Other writers have sought the explanation for this disease in an unusual difference between the ages of the parents; in a syphilitic taint in the child; in undue emotional stress on the part of the mother during the early period of the pregnancy; in hyperthyroidism in the fetus—in immaturity or senility of the ova and in endocrine disturbances in the mother.

The very fact that such diverse theories have been advanced is fairly reliable evidence that we have not yet arrived at the correct solution. A review of the literature will convince one of the fallacies of some of these hypotheses. For example, were syphilis the underlying cause, more observers would have discovered evidence of congenital syphilis in their cases. Such evidence is remarkably lacking in the clinical reports on Mongolian idiocy, although there have been writers who have claimed to have found it in a large proportion of their patients (145). At the Mayo Clinic, where the Wassermann reaction was sought as a routine measure in such cases, not one was found to show a positive Wassermann, although the series numbered 155 patients (125). Orel[131] who obtained the Wassermann reaction on 65 of his 95 patients chosen at random, found it uniformly negative. Such evidence forces us to look elsewhere for the cause of Mongolian idiocy.

Comby[103] has been an advocate of the theory that worry or physical suffering in the early months of pregnancy is responsible. In a series of 95 cases he elicited the history of distress, either physical or mental, in 69 instances. On the other hand, many women experience suffering in the early months of pregnancy, due to the pregnancy itself, and do not produce Mongolian idiots at the end of the time. During the World War, hundreds of women were subjected to the most unusual emotional and physical strain, but only a negligible number of them brought forth Mongolian imbeciles. This theory is wholly inadequate, and must be discarded.

The idea that the disease is caused by a marked discrepancy in the ages of the parents, as for example, when the father is much older than the mother, or the mother is older than the father, might find support from isolated instances. Tumpeer[152] recorded a patient whose father was 66 and whose mother was 38 at the time of his birth. Cautley[98] reports that the mother was 38 and the father 35 at the birth of his patient. But opposed to such cases are those in which the parents are both young, and with a normal difference between their ages. They may give birth not only to one Mongol, but to two; witness, Borovsky's[93] cases in which the mother was 26 and 28, and the father 31 and 33 at the birth of the first and second Mongol respectively. The average of a number of cases certainly lends no support to this view. Von Hofe,[116] recording 41 instances found that the father was older than the mother in 36 of them.

Orel[131] found the mother to be older than the father in only 22 out of 104 cases. In reports in the literature, I encountered 127 instances in which the father's age was given, with an average of 39.7 years. I found 321 reports which gave the mother's age, with an average of 34.3 years. Certainly here there is no indication of undue differences existing between the ages of the parents. This theory along with the other two must be ruled out of court.

Still another fallacy to be dealt with is that concerned with the idea that advanced age of the mother is responsible for the Mongolian idiot. Let us look at the statistics for a moment. In Shuttleworth's[144] series of 120 cases, 66 per cent were under forty and could not have been considered as too old for a pregnancy. In Comby's[103] series of 93 mothers whose ages were given or indicated, 67 per cent were under 40. Orel[131] found that in 104 instances, the mother of the Mongol was below 40 in 67 per cent of the cases. An even higher percentage of mothers was under 40 in von Hofe's series of 36, namely, 89.

Still [147] states that it is rare for a woman under 30 to give birth to a Mongol, only 17 instances occurring in his 420 cases. I found 73 times that the mother was under 30 in the 321 cases listed; so that 22.7 per cent of these women were decidedly young.

The most recent literature brings out a few other hypotheses, which because they are being advocated, should receive some attention here. Clark[101] advances the theory that hyperthyroidism in the fetus is the cause of Mongolism. This is of interest, because cases which have been reported of hyperthyroidism in the fetus or newborn have not mentioned any accompanying Mongolism, so that it cannot be a universal factor in its production. (158, 161, 162, 163.) As a matter of fact because of the close similarity between cretinism and Mongolian idiocy, the latter has been attributed to a deficiency in the thyroid during fetal life (112, 120), although thyroid administration has repeatedly failed to relieve this condition.

Mackintosh[120] attributes the disease to fertilization of ova that are immature or too senile to develop into a perfect fetus. He states that the Mongol is usually found as the first child of a very young mother, or one born when the mother is nearing the menopause. For cases that occur in between these ages, he postulates a pathological degeneration of the ovary occurring any time during the sexual life of the mother. In the combined 197 cases cited by Orel[131] and Comby[103] the mother was below 20 only twice, so that sexual immaturity played no part in these cases. With respect to the advanced age of the mother, we found 67 per cent under 40 with the average 34.3 years, an age removed from the time of the menopause by 10 or more years.

For all the cases not covered by the immature or senile aspects of his theory, Mackintosh brings forward the pathological degeneration of the ovary as an explanation. Since both ovaries may not

degenerate at once, he says that a woman may give birth to two, but only two Mongolian imbeciles in her life. The corollary of this proposition is that after the birth of the second Mongol, no child, normal or affected could be born. There are, however, records in which four Mongols in a family were born (90); and three in which three were present (48, 114, 140). In one instance (140) the three Mongols were preceded and followed by one normal child. In a second case, the defective offspring were the first, fourth and sixth of six children (114). In another family in which there were two Mongols, they were the first two children, and were followed by three normal ones. Mackintosh's theory of the etiology of Mongolism falls to the ground, condemned by recorded facts.

Armstrong[89] feels that the cause is maternal, operating at maturation. He does not state that he believes it to be hereditary in origin. Greig[112] considers that the disease has its origin in a defect in fetal growth. He conceives it to be an inability on the part of the fetus to continue development along the lines laid down in the early or embryonic period. While it is true that the effects of this disease may not be manifest until the fetal period, the primary cause was present I believe in the unfertilized ovum and in the sperm as well.

That the sperm is as much responsible as the ovum is supported by the pedigree reported by Hermann[114] in which the grandfather of one Mongol, and the grandmother of another were brother and sister. This is suggestive at least that the defective germ plasm was present in this brother and sister, and was passed on down to their grandchildren.

Now let us turn to what is perhaps the most favored of the theories, namely, that the Mongolian idiot is born at the end of a large family, and that the condition is due to reproductive exhaustion. After a rather thorough search through the literature, I was able to collect records of 275 cases of Mongolian idiocy in which the place in the family occupied by the defective child was stated. From these figures a curve was constructed showing the percentage of the total number of cases which occurred in each place in the family (Fig. 1 broken line). It will be noted that 28 per cent of all the cases were the first child in the family. Only 15 per cent of Still's[147] 420 cases, and 22 per cent of Orel's 95 cases were the first born of their families. This is an average of 20 per cent for the 788 cases listed in Still's, Orel's and my series.

Reference to this curve shows that 69 per cent of the number (190 cases) of affected patients were the result of the first four pregnancies, so that most of them could not have been attributed to reproductive exhaustion. In 300 cases reported by Reuben and Klein[127] (not included in my list), there were 50 per cent who were the result of the first three pregnancies. Although Still[147] is inclined to look upon the number of pregnancies as playing some rôle in the

production of this condition, his figures show that over half the cases, 54 per cent, fell into the place of the first four children of the family.

When we compute a curve for the entire families from which these patients came, we see that of the 1100 members making up these families, 738 or 67 per cent were the first four children of the family (Fig. 1, solid line). What does this very close approximation of figures mean: 69 per cent of the defectives and 67 per cent of the entire families occurring in the first four pregnancies? As I interpret them they mean this—the Mongolian idiot tends to occur in each place in the family in the same proportion that the population

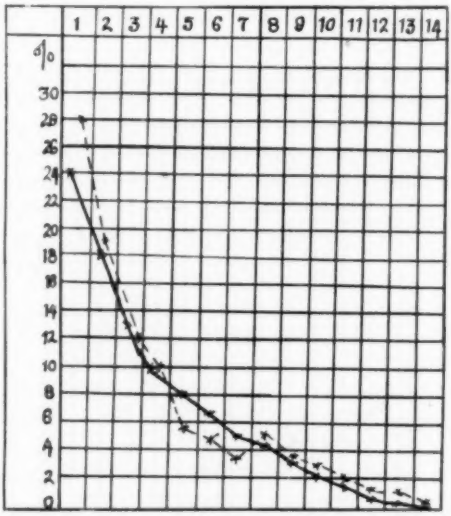


FIG. 1.—Based upon 275 cases of Mongolian idiocy, showing the percentages of the total number of cases which occur in each place in family, in broken line; while the solid line, based upon 1100 members which constituted the families from which the Mongols came, shows the percentages which occur in each place in family. Sixty-nine per cent of the affected and 67 per cent of the entire number occurred in the first four pregnancies.

as a whole occurs in these places, showing that there is no greater liability for the Mongol to be born at the end of a large family, than there is for it to appear at the beginning or middle of it.

We may attack this problem from a slightly different angle, namely, by determining the average pregnancy at which the defective offspring appeared. Brushfield[96] in his series of 157 cases (not included in my statistics) found that the average pregnancy which resulted in the birth of a Mongolian idiot was the fourth, the average from the 275 cases in the literature was 3.8. Although Still does not compute this figure it may easily be derived from his curve, the result being 4.9. There is thus remarkable uniformity in the values from three different series of cases.

Here might be mentioned the tendency to report the Mongol as the "last" child, implying that it comes at the end of the reproductive period of the mother. It might be the last child and yet be the result of the first pregnancy. Moreover, if there has been no time for a second pregnancy to supervene after the birth of the defective child, it is inevitably the "last" at that time. Hence statistics saying that it was the last child in 50 or 60 per cent of the cases do not prove anything at all. Von Hofe[116] points out this error and illustrates his point from his own series. Of 150 cases the Mongol was the last child in 97 cases, but in 70 of these 97, the child was under two years of age. There had scarcely been time for another pregnancy to occur. Were these families to be investigated ten

FIG. 2.—Showing the ratio of affected to normal individuals in each place in the family. The curve shows an upward trend at the end, but compare this with Fig. 6, based upon similar ratios in the case of families with 1600 members suffering from hereditary defects. These far from being looked upon as more apt to affect the later children have been held to be prone to affect the *first* child. The upward trend of both is explained by the few cases upon which the ratios in these places are founded.

years from now, the Mongol would stand less chance of being the last child. Berry[91] reports 10 instances in which a normal child followed the birth of the defective one. Brushfield[96] in 157 cases, found that six times the Mongol was followed by one normal infant; five times it was succeeded by two normal children; twice it was followed by three; once each by four, five and seven! If reproductive exhaustion be at the basis of this defect, what must have been the mother's condition after bearing seven more children following the Mongol! Comby[103] records 6 cases; Fletcher[110] one and von Hofe[116] one, in which the Mongolian idiot was followed by one or more normal children. Although these are by no means the only

instances in which the defective child was not the "last," they will suffice to show that this idea is without foundation in fact.

Ordahl[129] finds that twelfth children are affected four times as frequently as they are expected. In the series I have collected, those who are affected and fall in to the twelfth place in the family are twice as numerous as they should be according to the percentage in twelfth place in the entire family, but exactly the same thing holds true for the twelfth children in amaurotic idiocy. Thus 0.7 per cent of all the children in the Mongolian families were twelfth, but 1.4 per cent of the *affected* children were twelfth. But in amaurotic idiocy, the corresponding percentages are 0.3 for the population as a whole, and 0.6 for the affected children. The number of cases which one finds among twelfth children are so limited in number, because there are so few families which are that large, that statistics become unreliable. Thus in Fig. 2, which represents the ratio of affected to unaffected in the Mongol families, we see the curve rise sharply at the end, which might be interpreted to mean that the later pregnancies produce an unduly large proportion of the Mongols. But if we compare this with Fig. 4, which is similarly plotted for the ratios of affected to normal in amaurotic idiocy, we see this curve rises toward the end. Fig. 5 (reproduced from another paper which has not yet appeared in print) is a similar curve for 1600 cases of hereditary defects, and here again the curve which has varied on either side of a theoretical line representing the average for these percentages, rises abruptly for the thirteenth, fourteenth and fifteenth child. Yet such defects have been held as most liable to affect the *first* child of the family.[139] Thus we see that it is due to the limited number of cases found in these later pregnancies that the curve fluctuates so widely. The type of defect whose incidence is being shown in the curve, whether it be Mongolism, amaurotic idiocy or hereditary defects in general, does not appear materially to alter the shape of the curve (Fig. 2).

Summarized Objections to Theories of Etiology. To sum up briefly then the inconclusiveness of the theories thus far dealt with: syphilis, far from being universally found in these cases, is comparatively rare. There are too many instances in which the mother has endured physical or mental hardship during the pregnancy and does not produce a Mongol, for us to designate this as a cause. Most cases occur when the age differences between the parents is that usually found in the population at large. The average age of mothers producing Mongolian idiots was 34.3 years, and of the total number of cases, 22 per cent were less than 30. The average pregnancy which resulted in the defective child was about the fourth, and 69 per cent of the total number of defectives were found to occur in the first four pregnancies.

Mongolian Idiocy in Twins. But the fact which forces us to abandon all these arguments is not the statistics which show how old or

how young the mother was; or that it was the first or the fifteenth child who was the Mongol, but the fact that with the passing years, there are accumulating more and more instances in which at the time the Mongol is born, there is born also a normal twin.

It is at once obvious that if difference in age of the parents, or advanced age of the mother, or uterine exhaustion or endocrine disturbances (141) or any other environmental influence is to have any effect upon the developing fetus in the direction of producing a Mongolian idiot, then both twins should be affected. That they are not is a matter of record. Thus Mitchell and Downing[127] found that in 24 instances in which Mongolism had been reported in twins before 1926, there were only 3 cases in which both twins were affected. They were of the same sex. In the remaining 21 cases only one-half the contents of the uterus was affected, the other half being a normal twin.

Thus in the majority of instances the evidence is strongly against environmental influences, and much in favor of the defect being inherent in the germ cell, that is, inherited. This conception would at once explain the occurrence of twins one of which was normal, the other defective. But there comes in at this point the consideration of uniovular and biovular twins. If from two ova it is not necessary that they be alike, either in sex or characteristics, although they may be, but if they are derived from one ovum then they must be identical with respect to both these features. But we must remember that although the twins are of the same sex they are not necessarily from the same ovum. An article just published by H. H. Newman[160] discusses the method of diagnosing identical twins, and there are instances, even after the most exacting scrutiny, in which it is almost impossible to decide whether they are merely fraternal, or are identical. This must be remembered when we come to examine the reports of the cases in the literature. Since the report of Mitchell and Downing, I have collected 10 other cases in which this disease occurred in twins, and these with Mitchell's cases and 14 others reported by Orel[130] are tabulated in Table I.

There are listed here 48 cases of Mongolism in twins, involving one or both members. One of these (see Table I) is doubtful, the diagnosis between congenital syphilis and Mongolian idiocy not being clear. Of the 47 authentic cases, there are 17 in which the twins were of opposite sex, obviously biovular, and in which only one was affected. There were 6 cases in which both twins were affected and both were of the same sex, presumably uniovular. In 4 cases the sex was not given of either twin, but only one was affected. There were 20 cases (not including van der Bogert's) in which the twins were of the same sex, but only one was affected. In 5 of these the record says definitely that there were 2 placentæ or that they were biovular (108, 113, 127, and Moro and Siegert,

TABLE I.—MONGOLIAN IDIOCY IN TWINS.

Author.	Male.	Female.
Cases in which sex differed.		
Neumann, 1899 (cited by Orel, 1926)	■	○
Shuttleworth, 1909	□	●
Hultgren, 1915 (cited by Orel, 1926)	■	○
Cassel, 1917 (cited by Orel, 1926)	■	○
Cassel, 1917 (cited by Orel, 1926)	□	●
Swanberg and Haynes, 1919	■	○
McLean, 1922	■	○
Halbertsma, 1923	■	○
Halbertsma, 1923	■	○
Halbertsma, 1923 (cited by Orel, 1926)	■	○
Peiper, 1923 (cited by Orel, 1926)	□	●
Vas, 1925 (cited by Orel, 1926)	□	●
Orel, 1926	■	○
Comby, 1927	■	○
Comby, 1927	□	●
Krabbe, 1927 (cited by Orel, 1927)	□	●
Armstrong, 1928	■	○
Cases in which the sex was identical with one twin affected.		
Halbertsma, 1923	□ ■	
Halbertsma, 1923		○ ●
Siegert, 1923 (cited by Orel, 1926)		○ ●
Moro, 1923 (cited by Orel, 1926)		○ ●
Clay, 1922	□ ■	
Jewesbury, 1925		○ ●
Myers, 1925	□ ■	
Cassel, 1926* (cited by Orel, 1926)		
Orel, 1926		○ ●
Gautier and Coetaux, 1926 (cited by Orel, 1927)		○ ●
Coupland (cited by Greig, 1927)		○ ●
Coupland (cited by Greig, 1927)		○ ●
Dietrich and Berkley, 1926	□ ■	
Deitrich and Berkley, 1926		○ ●
Wieland, 1926 (cited by Orel, 1927)		○ ●
Mitchell and Downing, 1926	□ ■	
Chown, 1927	□ ■	
Krabbe, 1927 (cited by Orel, 1927)	□ ■	
Krabbe, 1927 (cited by Orel, 1927)		○ ●
Krabbe, 1927 (cited by Orel, 1927)		○ ●
Van der Bogert, 1916†	□ ■	
Cases in which twins were of same sex and both affected.		
Hjorth, 1906* (cited by Swanberg and Haynes)		
de Bruin, 1902 (cited by Halbertsma)	■ ■	
Strauch, 1923	■ ■	
Brückner, 1926		● ●
Reuben and Klein, 1926	■ ■	
Dickey, 1927	■ ■	

Cases in which sex of twins was unknown, one affected.

Fraser and Mitchell, 1877 (cited by Orel, 1926). Weigall (cited by Halbertsma). Halbertsma, 1923. McKee, 1919 (cited by Swanberg and Haynes).

* Sex not given.

† This case, in which one of male twins was affected, as well as an older sister of the twins, is doubtful, although Orel, 1926 includes them in his list as authentic cases. They were first shown as undoubted cases of Mongolian idiocy, but later as cases of congenital syphilis simulating Mongolism. The Wassermann test in the sister and affected twin was positive and negative in the normal twin brother.

cited by Orel[131]). In 14 of the remaining 15 cases, there is no evidence presented one way or another.

In Wieland's case, it is stated that they were diagnosed in the obstetrical clinic as *uniovular*. If this were true, it would be such strong evidence against the theory that this defect is hereditary that it would practically mean its abandonment. But Orel,[131] who cited this case, does not state whether Wieland gives the evidence upon which this diagnosis was made, and inasmuch as it is the only case in 47 that appears to controvert the evidence, I feel that we may take with considerably more than the traditional allowance of salt the statement that in this case the twins were from a single ovum.

Importance of the "Short Little Finger." Before going into a discussion of the mode of its inheritance, there is another matter that should be mentioned in this connection. In a great many of the clinical reports of Mongolian imbecility, mention is made of the presence of the short little finger, which does not reach up to the terminal joint on the ring finger; also of the incurved distal phalanx of the little finger; and in some instances the transverse line across the palm which divides it completely into two regions. Thursfield[151] in a study of his cases found that the incurved phalanx was absent in 16 cases, present in 13 and not noted in 13. Thus in the observed cases it was more often absent than present. Orel[131] found it present in 39 of 69 observed cases. Crookshank,[105] states that it has no special relation to Mongolism but occurs in the young of all races, and that not infrequently it is hereditary. I wish to mention here a family in which the short little finger with marked incurving of the last phalanx has been transmitted through the direct line for four generations, having been present in a woman, her daughter, two of her daughters, and a daughter of one of these. In addition to this, in the female of the fourth generation and in her mother there was present also the transverse line across the palm. Evidence as to the presence or absence of this feature in the other three was not noted. The intelligence in all these women was decidedly above the average. Wile[157] found this transverse line in 8 of 25 cases of Mongolism.

Wegelin[155] reported a family in which this defect, namely, a short little finger with the distal phalanx showing incurving, was transmitted with great frequency and as a dominant character. Orel[130] found that this condition had existed in four generations in the family which finally produced the Mongolian idiot which was one of his patients. The condition had been present in a woman, her son, six of his eleven children, and in two of the children of one of these who was affected, so that it behaved as a dominant character. Orel[130] cites the opinion of one writer that this condition in the hand may be indicative of a latent tendency toward Mongolism, which together with exogenous factors will produce outspoken Mongolian

idiocy. Although in Orel's case the mother who produced the Mongol had herself the deformed little finger, there was no exogenous circumstance that could account for the production of the defective child, especially since that pregnancy terminated in a normal child as well, and since the mother four years later produced another normal child.

Of course there are all grades of this defect, and a mere glance at the hands of many of the population serves to show how frequently the milder grades are seen. Certain it is that it is found in many individuals who are far from showing Mongolism, and that Mongolian idiots are frequently found in whom this particular characteristic is lacking.

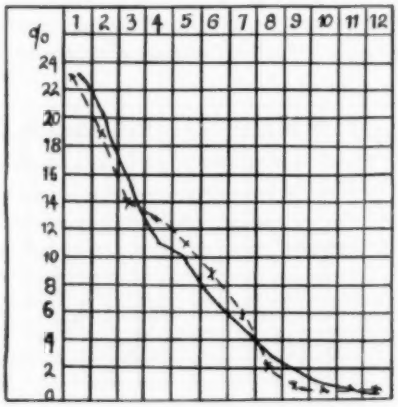


FIG. 3.—The solid line shows the percentages of the total membership of 118 families in which amaurotic idiocy occurred which fell into each place in family. The broken line represents similar percentages for the affected members of these families. Note the practical identity of the two curves, also that 69 per cent in both cases were the result of the first four pregnancies.

Method of Inheritance of Mongolian Idiocy. As noted in the foregoing paragraphs, there is good evidence in support of the theory that this condition is an hereditary one, and very conflicting evidence in support of any of the theories which attribute it to factors other than those residing in the germ cell. If it is inherited, what is the mode of its transmission; is it due to unit recessive factors as suggested by Hermann?[114,115]

If the reader will recall the matings of individuals showing dominant or recessive characters as worked out by Mendel over sixty years ago, he will remember that if a trait, normal or defective, be dominant, it must be present in at least one of the parents in order that it appear in the children. In the disease under discussion, there are, so far as I am aware, only two records of a Mongolian idiot having had a child (134, 139), and in these cases all three children were normal. In every instance in which a child was a Mongolian

idiot the parents were normal, at least as far as idiocy of the Mongolian type was concerned. That at once rules out the possibility of its being a dominant character. If the trait is recessive, there is one mating in which both parents being normal may yet produce a defective child, namely, that mating where both parents are hybrids, *DR*, and in which the offspring are apt to appear in the ratio of three normal children (*D D*, 2 *DR*) to one abnormal (*RR*). Such a unit recessive character Hermann[114,115] thinks Mongolism to be.

Let us examine the question with the aid of the statistics gathered from the literature, and compare these with the figures of other diseases due also to recessive factors, presumably unit. For comparison let us choose amaurotic family idiocy, which always appears in offspring of normal parents, and hence must be due to recessive characters. In the literature available to me, I was able to collect records of 118 families in which amaurotic family idiocy occurred,

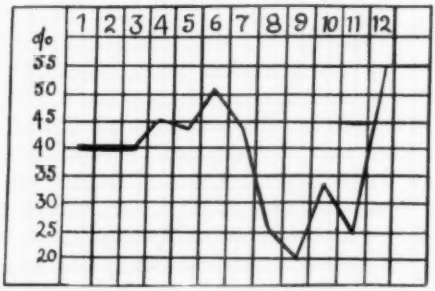


FIG. 4.—The ratio of affected to normal members in these 118 families. The curve rises at the end in a manner similar to that in Fig. 3 and Fig. 5.

and in which the order of the children was given. In addition to this there were 24 families recorded in which the order of children was not given. In Fig. 3 are plotted two curves, the broken line being the percentages showing the distribution of these affected individuals in the family. The curve for the place in family of all the members, affected and normal, is given in the solid line for comparison.

Thus in 118 families there was a total of 509 persons distributed through twelve places. Of these, 118, or 23 per cent, were the first born of their family; 100, or 20 per cent, were the second born, etc. The broken line represents a similar set of percentages for the affected persons in these 118 families. There was a total of 210 affected persons, of whom 48, or 23 per cent, were the first born; 40, or 19 per cent, were second born. A glance at Fig. 3 shows how closely these two curves approximate each other, indicating that there was no greater tendency for this disease to appear in the children from the earlier pregnancies than in those from the later ones,

or *vice versa*. Of these 509 persons, 354, or 69 per cent of the members, occurred in the first four pregnancies. Of the 210 defective children, 145, or 69 per cent, likewise occurred in the first four pregnancies. This shows again, as do the two curves, that in a family in which this disease is apt to occur, any one child is just as liable to show it as any other.

It was mentioned above that, in addition to the 118 families in which place in family was given, there were 24 other families found in which the disease occurred. Of these 142 families there were 68 in which only one child in the family was affected, and 74 families in which more than one was affected, distributed as follows: 29 had 2 defective children, 29 had 3; 11 had 4; 3 had 5; 1 had 6 and 1 had 8 amaurotic family idiots to its credit! Thus, of the total number of families listed, 74, or one family in every 1.9 families, had more than one member affected. These 142 families had a total of 279 affected children, or an average of 1.96 to a family.

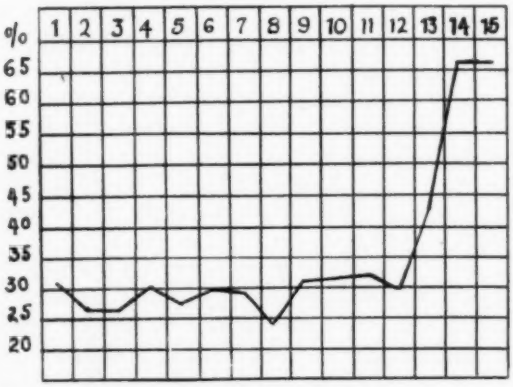


FIG. 5.—The ratio of affected to normal individuals in families in which occurred 1600 persons with hereditary defects. The same rise at end of curve as seen in Fig. 3, due to limited number of cases found in these later pregnancies.

Let us now compare these figures with those obtained in an exactly similar manner for Mongolian idiots, a disease far more frequent than amaurotic idiocy, for where I found only 142 families affected with the latter condition, I found records of 2491 families in which Mongols had been born. Of these the place in the family was indicated in 268 instances; the number of affected being 275. Fig. 1 gives the curve for the place in family of all the members in a solid line, and a similar curve for only the affected persons in these families in the broken line. Again there will be noted a rather close agreement between the two, thus indicating that there is not any undue tendency for the Mongol to appear in the later pregnancies. As a matter of comparison, 190 of the affected children, or 69 per cent occurred in the first four pregnancies, while 738, or 67 per cent

of the children of these families were the first four of the family. It will be noted that just the same percentage of Mongols as of amaurotic idiots appeared in the first four pregnancies, namely, 69. Still's standard curve shows that only 63 per cent of the whole population occurs in the first four pregnancies. There never has been held to be any special predilection on the part of the late pregnancies to terminate in an amaurotic idiot; there should be no theory that the Mongolian idiot is more apt to occur at the end of a large family in the face of figures like these.

Of these 2491 families, in which occurred 2526 Mongolian idiots, there were 2461 in which only one child was affected, and but 30 in which more than one was a Mongol. There was one instance in which four were affected (90); three in which three Mongols appeared (48, 114, 140); and 26 families in which there were two Mongols (93, 104; 108; 111 same as 132; 114, 2 cases; 123; 132; 137; 140; 142; 145; 154, 130, 9 cases; 131, five cases). In addition to these cases in which brothers and sisters were affected, there were three instances in which first cousins were affected (93, 99, 133), one in which second cousins were Mongolian idiots, (114) and one instance in which a woman who had two sisters and one brother affected, gave birth to a child similarly afflicted (114). Thus, although there was one family in every 1.9 which showed familial distribution in amaurotic family idiocy, there was only one in every 83 families which showed more than one child affected with Mongolian idiocy. While the average number of affected per family in the former disease was 1.96, it was only 1.014 for the latter.

Even the most casual glance at these figures will convince the average reader, that if both these diseases are due to recessive factors, amaurotic family idiocy is due to factors which make the appropriate combination far more frequently than do those responsible for Mongolian idiocy; almost 44 times as often according to the above figure. What then is the explanation of the wide difference in the two diseases, one occurring frequently in families, the other rarely, since both are stated to be hereditary, and due to recessive factors?

Let us assume for the moment (a statement that has indeed been assumed for a long time) that amaurotic family idiocy is due to a combination of two recessive factors, RR. Since it always occurs in the children of healthy parents (for the affected child always dies in infancy and never lives long enough to become a parent) the parent's genetic constitution must be DR, so that the chances are 1 in 4 that the defective child will be born; 3 in 4 that the children will be normal. Do the figures of amaurotic family idiocy agree with these theoretical ones? We found that of 509 persons, 210 were affected, or 41 per cent. We should have expected only 25 per cent. Where is the difficulty?

From statistics gathered in connection with hereditary conditions

in which the number of families having 1, 2, 3, and so forth, children was determined, I found that in a total of 200 families, there were 41 with only one child, 33 with two; 28 with three; 22 with four; 18 with five; 15 with six; 12 with seven; 9 with eight; 8 with nine; 5 with ten; 4 with eleven; 2 with twelve; and one each with thirteen, fourteen and fifteen children respectively.

Experimental Studies. I then set myself the task of determining how many children with amaurotic family idiocy would be born in 200 families, in which the genetic constitution of the parents was *DR* and in which one would expect that one in every four would be defective. The method chosen was simple and not without errors. It is not even thought that such a procedure as that to be described proved the method of inheritance in amaurotic family idiocy or in Mongolian idiocy. The results obtained were interesting, however, when compared with the figures obtained from the literature of actual cases.

For the so-called theoretical cases of amaurotic family idiocy, I chose three red balls, and one white; placed them in a box, in the bottom of which was a hole slightly larger than the diameter of the balls, which were of the same size and weight. These were then shaken up, the box turned upright and a ball allowed to roll out. If red, it was regarded as a normal child, if white it was listed as defective. This was done 847 times (that being the total number of individuals in the 200 families mentioned above). These were divided off into families of appropriate size, and the position of the defective child in its respective family noted. Thus, of the 200 families in which the white ball might have appeared, it did so in only 122, but appeared in these 122 families 205 times. There were 68 in which the white ball appeared only once, and 54 in which it appeared more than once. Thus there was one in every 2.2 families affected, a number not far off the 1.9 actually found from the literature. These 122 families had 205 affected, an average of almost 1.7 to a family—a number, again, not far from the actual 1.96 per family. There were 143, or 69 per cent of these 205 cases that occurred in the first four pregnancies, exactly corresponding with the percentage actually found for that value.

Now it will be recalled that there were 847 opportunities for the white ball to appear; it actually came out 205 times, or once in every 4.1 times as against the theoretical 1 in 4. The law of chance was working rather smoothly here. On the other hand, the 205 times were grouped in 122 families, with a total membership of 661. This means that instead of 25 per cent of these families there was here 31 per cent, affected. Compare this with the high value of 41 per cent found in the real families. This explanation is probably the one at the basis of the too high percentages in actual cases. We do not know the number of families who have the potentiality of producing an amaurotic idiot who do not do so. If we did, and added

the number of pregnancies in them which result in normal children to our calculations, we should inevitably find a decrease in the value of 41 per cent. What this decrease would be is, of course, impossible to say. The close agreement between these theoretical families and those found in the literature is interesting to those who believe that this condition is inherited and is due to a combination of unit recessive factors.

It will be recalled that Mongolian idiocy though much more frequently encountered than amaurotic family idiocy, is, however, very rarely familial in distribution as compared with the numerous instances in which amaurotic idiocy affects more than one member of the family. Were it due to a unit recessive factor, its chances of affecting more than one child in a family would be identical with amaurotic idiocy, and so we should expect to find that instead of 30 families with more than one Mongol, there would be 1311 families showing familial distribution. Obviously, Mongolian idiocy is *not* due to a pair of *unit* recessive factors.

If we suppose that it may be due to a combination of two pairs of recessive factors then the chances for its appearing in more than one member of a family would be lessened, the degree to which that lessening took place depending upon the genetic constitution of the parents. For example, let us suppose that there are two factors, *A* and *B*, dominance of which is expressed by capitals, recessiveness expressed by small letters, and that it is only when the genetic constitution of the individual is *aabb* that Mongolism results. Then the parents could be a combination of any of the following constitutions; (1) *Aa Bb*; (2) *aa Bb*; (3) *Aabb*, each one of which would be normal, in itself, but capable of producing a Mongol if the proper combination were made. The percentages of defective offspring would vary according to the combination of parents.

In Table II one sees that of the six possible combinations, there are three which give chances of 1 in 4 for the appearance of the defective offspring, *aabb*, two in which the chances are 1 in 8, and one in which they are 1 in 16. If these three parental types were present in equal numbers in the community, and if the 6 possible combinations of these types were made in equal numbers, the chances for the Mongol to appear in these families as a whole would be 1 in 7.

Taking the combination which produced Mongolian idiots in the ratio of one idiot to 15 normal individuals, as the basis for the theoretical families, the balls were now placed in the box, 15 red and one white one, and the series of 200 families completed as has been described. Here out of a possible 200 families in which the defective child might have occurred, it actually appeared in but 50. In these 50 families there were 6 in which the white ball appeared more than once. Thus, one family in every eight showed familial distribution. There was a total of 59 affected, or an average of 1.18 to a family. That there was adequate mixing of the balls, so that

the law of chance had full sway, is shown by the fact that of the total number of balls thrown out (847) only 59 times did the white ball appear. One-sixteenth of 847 is 53, so that the number 59 is not far off the theoretical value.

It will be noted, however, that these theoretical figures indicate that there should be several members of a family affected far more frequently than there are actually. Hence we may conclude that the inheritance of Mongolian idiocy is a much more complicated matter than dependence upon unit recessive factors or upon two pairs of recessive factors. As was noted above, it is sometimes associated with the presence of peculiarities in the hand that are definitely inherited in some families, apparently as simple dominant characters. Whether associated with several recessive characters,

TABLE II.—COMBINATIONS OF TWO PAIRS OF RECESSIVE CHARACTERS.

COMBINATION 1 BY 1.

	egg AB	Ab	aB	ab
sperm AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

COMBINATION 1 BY 2.

	egg AB	Ab	aB	ab
sperm aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

COMBINATION 1 BY 3.

	egg AB	Ab	aB	ab
sperm Ab	AABb	AAbb	AaBb	Aabb
ab	AaBb	Aabb	aaBb	aabb

COMBINATION 2 BY 2.

	egg aB	ab
sperm aB	aaBB	aaBb
ab	aaBb	aabb

COMBINATION 2 BY 3.

	egg Ab	ab
sperm aB	AaBb	aaBb
ab	Aabb	aabb

COMBINATION 3 BY 3.

	egg Ab	ab
sperm Ab	AAbb	Aabb
ab	Aabb	aabb

there are one or more dominant characters, will remain a mystery, inasmuch as we cannot make the appropriate mating experiments for the solution. It is interesting to speculate, however, concerning the mode of inheritance, and inasmuch as there are numerous instances of Mongolian idiocy in which these hand peculiarities are lacking, it may be that it is dependent upon recessive factors alone, unassociated with the presence of any dominant factors.

For the sake of carrying the analysis a step further, let us assume that the condition of Mongolism is dependent upon the simultaneous presence in the mature germ cell of *three* pairs of recessive factors carried in three different chromosomes. Then the chances for the meeting of the factors to produce the proper combination, *aabbcc*, are only 1 in 64 if the parents are both hybrids with respect to all three factors. As in the case of the two pairs of factors, there are other combinations possible, but inasmuch as they all give more frequent opportunity for the combination representing the defective one, they will be disregarded for the moment.

When choosing the balls which should represent the combination

in which the chance for the defective offspring to appear was 1 in 64, the 63 colored balls were chosen of seven different shades, so that I might judge by the color which came out each time if there were adequate mixing of the balls in the box, a fact I could not have decided had they all been of the same color with the exception of the white one. With increase of the difficulties attendant upon the appearance of the white ball, the number of times which it appeared in the set of 200 families became so small as to make results unreliable; so that instead of 200 families with a total of 847 members, the occurrence of this defect was sought in 600 families with a total of 2541 members. In the first 200, the white ball came out 13 times, in the second 200, 14 times, and in the third 200, 13 times, but twice it occurred in the same family. Thus it occurred 40 times in 39 families, or an average of 1.02 to a family, a value in close agreement with that actually found, namely, 1.014.

That there was adequate mixing of the balls is shown by the fact that one-sixty-fourth of 2541 is 39.7, while the actual number obtained was 40. One family in 39 showed familial distribution as compared with 1 in 83, actually found from the literature. This "familial" instance, however, did not occur until I had come to the thirty-eighth family with an affected member. Hence it might well have been that had I made another attempt to find how often it occurred in a second 600 families, I might have gone well up toward the 80 mark before encountering a second "familial" case.

Further Discussion. But, as was mentioned, the combination of parents in which the chances for a defective offspring are 1 in 64 is by no means the only possible one. There are seven possible types of parents, *Aa BbCc*, *Aa Bbcc*, *AabbCc*, *Aabbcc*, *aa BbCc*, *aa Bbcc*, *aabbCc*, with 28 possible types of matings. The chances range in these from 1 in 4 to 1 in 64, If these seven types occurred with the same frequency, and the 28 varieties of mating were made equally often, the chances for the Mongol to appear in the group as a whole would be 1 in 14. As there is no reason to suppose that the only combination of parents producing the Mongol is the one in which the parents are hybrid for each of the factors in question, namely, *Aa BbCc*; even this combination of three recessive factors gives a higher frequency of appearance than we actually find; for it must be remembered that in choosing the conditions of 1 in 64 the combination was taken that gave the least chance of producing the defective child.

If we now take four recessive characters, and determine the chances of all four coming together in the same individual, we find first that there are 15 types of parents who could produce the desired combination of characters, and these might be grouped in 120 different combinations. Here the chances range from 1 to 4 in ten of the matings to 1 to 256 in one of the matings. Again, assuming that all 120 matings are made with the same frequency, the chances that the Mongol would appear in these families would be 1 in 30.

If we now choose five recessive factors as the basis of the defect, we find that there are 31 possible types of parents, all normal themselves, but capable of producing the desired combination of factors, *aabbccddee*. There are 486 possible combinations of these 31 types. in which the chances of having the defective child appear, range from 1 to 4 in some of them to 1 to 1024 in one. Assuming that all 486 combinations are made with the same frequency, the chances for the Mongol to appear in the group are 1 in 63.

Although this is in almost exact agreement with the conditions chosen, 1 in 64, and although these theoretical values were in close approximation to those found by dealing with the recorded cases of Mongolism, it is apparent how impossible it is to say that this defect is due to a combination of five recessive factors. We do not know the genetic constitution of the parents, and we do not know with what frequency the various combinations are made. Any deviation from the equality in number of all types of parents that was at the basis of the estimations made above would of course cause the chances of the Mongol appearing either to be much less or much greater than the number given. Such theoretical considerations, however, although not affording any proof of the mode of inheritance of Mongolism, do bring very clearly before us an explanation of how a condition dependent upon a number of factors, can be so infrequent in most families, that it appears only as isolated cases, while in other families it may affect as many as four out of ten children (90). In such an instance, each parent would have almost the entire combination of factors present in his germ cells, but be saved from being a Mongol himself by the presence of one of the factors in the dominant condition, as, for example, *aabbccDdee*.

Another combination of factors which approximates these results closely is one of two dominant and four recessive factors. The affected person might be homozygous or heterozygous for one or both of the dominant factors, but homozygous for all the recessive ones. There are 140 possible types of parents, with over 8000 possible types of matings. Assuming that these matings were all made with the same frequency, the chances for the Mongolian imbecile to appear would be 1 in 70. This value is close to 1 in 63, and might explain the results found from cases in the literature as well as that based upon the assumption that the disease is due to the presence of five pairs of recessive factors.

It must not for a moment be assumed that this method of attacking the problem is looked upon as amounting to proof of any theory whatever. It is merely put forward as of interest that the theoretical values obtained are in such close agreement with those obtained by cases from the literature, both with respect to amaurotic family idiocy, which has been looked upon as due to unit recessive factors, and with respect to Mongolian idiocy which corresponds to those results obtained when the assumption was made that it was dependent upon five pairs of unit recessive factors, or two dominant and

four recessive factors. Although these theoretical considerations have not proved how Mongolism is inherited, they at least prove that it is *not* due to a pair of unit recessive factors, as has been suggested. [114,115]

After this paper had been prepared and was ready for publication, reference was found to Orel's papers[131,130] which were procured and his statistics incorporated in the text. It was found that he, too, says that Mongolian idiocy is due, not to one factor, but to a row of factors, in the germ cells.

Conclusions. From a survey of the literature dealing with Mongolian idiocy, I conclude that no adequate support for the contentions that syphilis, mental or physical suffering of the mother during pregnancy, advanced age of the mother at the time of conception, reproductive exhaustion due to a large number of pregnancies, or to the father being younger or much older than the mother have any etiologic significance in the production of this disease.

Evidence is presented that these and all other environmental influences that may be mentioned are not the cause of Mongolian idiocy, but that it is due to inherited defects, and so is germinal in origin.

There is no support for the statement that it is due to the presence of one pair of unit recessive factors.

Its mode of inheritance appears to be much more complex, and figures are given showing the similarity between theoretical and actual results when the theoretical are based upon the assumption that the disease is due to the simultaneous presence in the germ cell of five pairs of recessive factors or two dominant and four pairs of recessive factors, carried in as many different chromosomes. It is not, however, suggested that such agreement constitutes proof that this is the mode of inheritance of Mongolian idiocy.

Appendix. When a factor is spoken of in this paper as being responsible for a disease, it is not to be understood that the term "factor" is synonymous with "gene." It merely refers to that group of determiners, be they one or many, residing in one chromosome, which are responsible in whole or in part for the appearance of the particular disease in question.

Jennings has objected to the term "unit character," because he says that eye color, for example, which has been designated as a unit character, may in reality depend upon as many as 50 genes, absence of any one of which would interfere with the appearance of red eyes. Thus a fly may have 49 of the necessary genes for red eye color. but show white eyes through the lack of 1 gene. It is, therefore, not a unit character. To conceive of such complex qualities, as mental states, for example, as dependent upon a single gene or several genes is impossible, he says. This is quite true, but since there are only a limited number of chromosomes, it becomes evident that many genes are located in one chromosome. If *all* the genes responsible for the disease, let us say, are located in the *same* chromosome, then it may be termed a unit character in the sense that in the process of transmission, that disease will be passed on in the same manner that it would have been were it determined by one gene alone.

Jennings' conception that these so-called unit characters are dependent upon the presence of many genes, some of which may be lacking in one person, others lacking in another whose genetic constitution is thus differ-

ent despite their possessing the same somatic character, is of great help in the interpretation of what might otherwise seem to be irregularities in the transmission of various characters. Thus, as Jennings points out, a character that behaves as a dominant in one family may act as a recessive in another, a fact difficult to explain if the character is conceived to be due to one gene alone.

Applying this idea to the above discussion merely means that the genes, no matter what their number may be, which are responsible for the appearance of the disease known as Mongolian imbecility are probably located in as many as five or six different chromosomes. "Factor" refers merely to the group of genes which are held in one chromosome.

After this paper was prepared, a book by Brousseau and Brainard entitled "A Study of the Physical and Mental Characteristics of Mongolian Imbeciles" appeared. They reach the conclusions stated in the above paper, that none of the theories advanced as to its cause are adequate. They postulate an endocrine dysfunction in the patient himself. Heredity has no part in its production, since the family history is usually good, so they state. That endocrine disturbances may be the cause of it I admit, but if so, heredity is at the basis of the inadequate endocrine system.

BIBLIOGRAPHY.

Amaurotic Idiocy.

1. Abt, I. A.: Am. J. Dis. Child., 1911, **1**, 59.
2. Adie, W. J.: Proc. Roy. Soc. Med., 1923, **17**, Neurol. Sec., 58.
3. Adie, W. J.: Ibid., 1925, vol. **19**, Sec. Dis. Child., p. 1.
4. Batten, F. E.: Trans. Ophth. Soc. U. K., 1903, **23**, 386.
5. Batten, F. E.: Proc. Roy. Soc. Med., 1915, **8**; Sec. Dis. Child., 89.
6. Batten, F. E., and Mayou, M. S.: Ibid., Ophth. Sec., 71.
7. Buchanan, M.: Ann. Ophth., 1907, **16**, 249.
8. Carlyll, H. B., and Mott, F. W.: Proc. Roy. Soc. Med., 1911, **4**, Path. Sec., 147.
9. Clark, H. S.: J. Am. Med. Assn., 1918, **71**, 1799.
10. Cockayne, E. A., and Atlee, J.: Proc. Roy. Soc. Med., 1915, **8**, Ophthl. Sec., 65.
11. Cohen, M.: J. Am. Med. Assn., 1907, **48**, 1751.
12. Cohen, M.: Arch. Ophth., 1923, **52**, 140.
13. Coriat, I. H.: Arch. Ped., 1913, **30**, 404.
14. Cotton, A. C.: Ibid., 1902, **19**, 17.
15. Drummond, W. B.: Lancet, 1907, i, 1432.
16. Epstein, J.: New York Med. J., 1917, **106**, 887.
17. Epstein, J.: Med. Rec., 1920, **97**, 224.
18. Epstein, J.: Med. J. and Rec., 1924, **120**, 123 in supp.
19. Epstein, J.: Arch. Ped., 1925, **42**, 236.
20. Fairbanks, A. W.: Ibid., 1907, **24**, 768.
21. Feingold, M.: Arch. Ophth., 1916, **45**, 533.
22. Frank, M.: J. Am. Med. Assn., 1906, **46**, 187.
23. Frets, G. P., and Overbosch, J. F. A.: Ibid., 1923, **81**, 2158.
24. Gifford, H.: Ophth. Rec., 1912, **21**, 577.
25. Goldstein, I.: Arch. Ped., 1906, **23**, 616.
26. Goldstein, I.: Am. J. Obst., 1908, **58**, 169.
27. Goldstein, I.: Ibid., 1909, **61**, 554.
28. Gordon, A.: New York, Med. J., 1907, **85**, 294.
29. Greenfield, J. G., and Holmes, G.: Brain, 1925, **48**, 183.
30. Hassin, G. B.: Arch. Neur. and Psych., 1924, **12**, 640.
31. Hassin, G. B.: Ibid., 1926, **16**, 708.
32. Hassin, G. B., and Parmelee, A. H.: Am. J. Dis. Child., 1927, **35**, 87.
33. Heiman, H.: Arch. Ped., 1897, **14**, 268.
34. Heiman, H., Bookman, S., and Crohn, B. B.: Trans. Am. Ped. Soc., 1912, **24**, 62.
35. Hermann, C.: Arch. Ped., 1915, **32**, 902.
36. Higier, H.: Neurol. Centralbl., 1901, **20**, 843.
37. Hine, M. L.: Proc. Roy. Soc. Med., 1922, **16**, Ophth. Sec., 18.

38. Hoppe, L. D., and Clay, G. E.: Arch. Ped., 1924, **41**, 389.
39. Howard, A. C. P.: Mont. Med. J., 1910, **39**, 429.
40. Huismans, L.: Deutsch. med. Wchnschr., 1906, **32**, 1737.
41. Hymanson, A.: Arch. Ped., 1913, **30**, 825.
42. Jacobi, A.: Ibid., 1898, **15**, 561.
43. Ledbetter, T. A.: Canadian Med. Assn. J., 1925, **15**, 367.
44. Levy, A. H.: Proc. Roy. Soc. Med., 1922, **16**, Ophth. Sec., 17.
45. MacGregor, R. R.: Canadian Med. Assn. J., 1926, **16**, 1362.
46. McHenry, J. H.: Arch. Ped., 1917, **34**, 161.
47. McKee, J. H.: Am. J. Med. Sci., 1905, **129**, 22.
48. Malkin, B.: Abs. in Bib. Eugenica, 1928, **1**, 148.
49. Mandel, L.: Proc. Roy. Soc. Med., 1922, **16**, Sec. Dis. Child., 55.
50. Marinesco, G., and Radovici, A.: L'Encephale, 1923, **18**, 145.
51. Mayou, M. S.: Proc. Roy. Soc. Med., 1907, **1**, Neurol. Sec., 98.
52. Nardin, W. H., and Cunningham, R. S.: Am. J. Ophth., 1923, **6**, 476.
53. Nettleship, E.: Trans. Ophth. Soc. U. K., 1908, **28**, 76.
54. Neurath, R.: Wien. klin. Wchnschr., 1915, **28**, 1361.
55. de Nicolo, F.: Arch. de méd. des enfants, 1927, **30**, 545.
56. Oatman, E. L.: Am. J. Med. Sci., 1911, **142**, 221.
57. Parhon, C., and Goldstein, M.: Rev. Neurol., 1909, **2**, 895.
58. Paterson, D.: Proc. Roy. Soc. Med., 1921, **15**, Sec. Dis. Child., 46.
59. Paton, L.: Ibid., 1923, **17**, Ophth. Sec., 42.
60. Poynton, F. J.: Brain, 1906, **29**, 180.
61. Poynton, F. J., and Parsons, J. H.: Trans. Ophth. Soc. U. K., 1905, **25**, 312.
62. Poynton, F. J.: Proc. Roy. Soc. Med., 1909, **2**, Clin. Sec., 127.
63. Price, G. E.: J. Am. Med. Assn., 1914, **62**, 1545.
64. Pusey, B.: Trans. Am. Ophth. Soc., 1915, **14**, 364.
65. Rand, C. W.: J. Am. Med. Assn., 1918, **70**, 55.
66. Russell, J. S. R.: Proc. Roy. Soc. Med., 1923, **17**, Neurol. Sec., 57.
67. Sachs, B., and Strauss, I.: J. Exp. Med., 1910, **12**, 685.
68. Sachs, B.: New York Med. J., 1896, **63**, 697.
69. Sachs, E.: Johns Hopkins Hosp. Bull., 1904, **15**, 94.
70. de Sanctis, A. G.: Internat. Clinics, 1922, ser. 32, **4**, 225.
71. Sheffield, H. B.: Med. Rec., 1912, **81**, 165.
72. Smith, E. B.: Proc. Roy. Soc. Med., 1910, **3**, Sec. Dis. Child., 148.
73. Smith, R. M.: Boston Med. and Surg. J., 1912, **166**, 370.
74. Spielmayer, W.: Neurol. Centralbl., 1906, **25**, 51.
75. Starck: J. Am. Med. Assn., 1920, **75**, 643.
76. Sterling, W.: Neurol. Centralbl., 1906, **25**, 55.
77. Taft, A. E., and Munroe, J. P.: Am. J. Psych., 1925, **5**, 89.
78. Talbot, F. B.: Am. J. Dis. Child., 1918, **16**, 39.
79. Tay, W.: Trans. Ophth. Soc. U. K., 1881, **1**, 55.
80. Turner, J.: Proc. Roy. Soc. Med., 1912, **5**, Path. Sec., 117.
81. Verhoeff, F. H.: Arch. Ophth., 1909, **38**, 107.
82. Wadsworth, O. F.: Trans. Am. Ophth. Soc., 1885, p. 572.
83. Wandless, H. W.: New York Med. J., 1909, **89**, 953.
84. Weber, F. P.: Proc. Roy. Soc. Med., 1910, **3**, Sec. Dis. Child., 59.
85. Weber, F. P.: Ibid., 1916, **10**, Sec. Dis. Child., 100.
86. Welt-Kakels, S.: Arch. Ped., 1908, **25**, 471.
87. Wolfsohn, J. M.: Arch. Int. Med., 1915, **16**, 257.
88. Wyllie, W. G.: Proc. Roy. Soc. Med., 1925, **18**, Sec. Dis. Child., 70.

MONGOLIAN IDIOCY.

89. Armstrong, H.: Brit. Med. J., 1928, i, 1106.
90. Babonneix, L., and Villette, J.: Arch. de méd. des enfants, 1916, **19**, 478.
91. Berry, D. M.: Brit. J. Dis. Child., 1924, **21**, 259.
92. Bleyer, A.: J. Am. Med. Assn., 1925, **84**, 1041.
93. Borovsky, M. P.: Ibid., 1928, **90**, 459.
94. Brahdy, M. B.: Arch. Ped., 1927, **44**, 724.
95. Brückner: Deutsch. med. Wchnschr., 1926, **52**, 1279.
96. Brushfield, T.: Brit. J. Dis. Child., 1924, **21**, 241.
97. Cautley, E.: Proc. Roy. Soc. Med., 1909, **2**, Sec. Dis. Child., 126.
98. Cautley, E.: Ibid., 1913, **6**, Sec. Dis. Child., 133.
99. Chotzen: Monatschr. f. Kinderheilk., 1925, **30**, 120.
100. Chown, G.: Canadian Med. Assn. J., 1927, **17**, 943.

101. Clark, R. M.: J. Ment. Sci., 1928, **74**, 265.
102. Clay, H. T.: Arch. Ped., 1922, **39**, 726.
103. Comby, J.: Arch. de méd. des enfants, 1927, **30**, 86.
104. Cozzolino, O.: La Pediatria, 1926, **29**, 49.
105. Crookshank, F. G.: Proc. Roy. Soc. Med., 1913, **6**, Sec. Dis. Child., 133.
106. Crookshank, F. G.: Ibid., 1914, **7**, Sec. Dis. Child., 79.
107. Dickey, L. B.: California and West. Med., 1927, **26**, 344.
108. Dietrich, H., and Berkley, H. K.: Ibid., 1926, **24**, 498.
109. Effler: Deutsch. med. Wchnschr., 1907, **33**, 444.
110. Fletcher, M. H.: Proc. Roy. Soc. Med., 1909, **2**, Clin. Sec., 194.
111. Glassburg, J. A.: J. Am. Med. Assn., 1924, **82**, 1196.
112. Greig, D. M.: Edinburgh Med. J., 1927, **34**, 253, 321.
113. Halbertsma, T.: Am. J. Dis. Child., 1923, **25**, 350.
114. Hermann, C.: Arch. Ped., 1917, **34**, 494.
115. Hermann, C.: Ibid., 1925, **42**, 523.
116. von Hofe, F. H.: Ibid., 1922, **39**, 737.
117. Imrie, G. T.: Am. J. Obst., 1913, **67**, 1240.
118. Jeremy, H. R.: Proc. Roy. Soc. Med., 1920, **14**, Sec. Dis. Child., 11.
119. Jewesbury, R. C.: Ibid., 1925, **18**, Sec. Dis. Child., 49.
120. Keith, Sir Arthur: Johns Hopkins Hosp. Bull., 1922, **33**, 195.
121. Langmead, F.: Proc. Roy. Soc. Med., 1909, **2**, Clin. Sec., 190.
122. Langmead, F.: Ibid., 1919, **12**, Sec. Dis. Child., 95.
123. Mackintosh, J. M.: Brit. Med. J., 1928, ii, 129.
124. McLean, S.: J. Am. Med. Assn., 1922, **78**, 13.
125. Mebane, D. C.: Am. J. Dis. Child., 1924, **28**, 438.
126. Midelton, W. J.: Proc. Roy. Soc. Med., 1914, **7**, Sec. Dis. Child., 184.
127. Mitchell, A. G., and Downing, H. F.: Am. J. Med. Sci., 1926, **172**, 866.
128. Myers, B.: Proc. Roy. Soc. Med., 1925, **18**, Sec. Dis. Child., 69.
129. Ordahl, G.: J. Hered., 1927, **18**, 429.
130. Orel, H.: Ztschr. f. Kinderheilk., 1926, **42**, 440.
131. Orel, H.: Ibid., 1927, **44**, 449.
132. Pardee, I. H.: J. Am. Med. Assn., 1920, **74**, 94.
133. Pogorschelsky, H.: Monatschr. f. Kinderheilk., 1924, **28**, 65.
134. Pogue, M. E.: Illinois Med. J., 1917, **32**, 296 (cited by 108.)
135. Poynton, F. J.: Proc. Roy. Soc. Med., 1909, **2**, Clin. Sec., 188.
136. Provinciali, U.: Pediatria, Naples, 1916, **24**, 403.
137. Reuben, M. S., and Klein, S.: Arch. Ped., 1926, **43**, 552.
138. Rolleston, J. D.: Proc. Roy. Soc. Med., 1916, **9**, Sec. Dis. Child., 65.
139. Rosenberg, L.: Wien. med. Wchnschr., 1924, **74**, 2503 (cited by Orel, 1926).
140. Vander Scheer, W. M.: Nederl. Tijdschr. v. Geneesk., 1919, **1**, 328.
141. Schlapp, M.: J. Hered., 1925, **16**, 161.
142. Scott, Z. R.: Atlantic Med. J., 1923, **27**, 841.
143. Shaw, J. J.: Proc. Roy. Soc. Med., 1914, **7**, Sec. Dis. Child., 146.
144. Shuttleworth, G. E.: Brit. Med. J., 1909, ii, 661.
145. Stevens, H. C.: J. Am. Med. Assn., 1915, **64**, 1636.
146. Stewart, R. M.: Proc. Roy. Soc. Med., 1926, **19**, Psych. Sec., 11.
147. Still, G. F.: Lancet, 1927, ii, 795, 853.
148. Strauch, A.: J. Am. Med. Assn., 1923, **81**, 2181.
149. Sutherland, G. A.: Proc. Roy. Soc. Med., 1909, **2**, Clin. Sec., 187.
150. Swanberg, H., and Haynes, H. A.: Arch. Neur. Psych., 1919, **1**, 717.
151. Thursfield, H.: Brit. J. Child. Dis., 1921, **18**, 18.
152. Tumpeer, J. H.: J. Am. Med. Assn., 1922, **79**, 14.
153. de Vaugiraud, M.: Arch. de méd. des enfants, 1922, **30**, 158.
154. Wachenhaim, F. L.: Am. J. Obst., 1913, **67**, 1036.
155. Wegelin: Berl. klin. Wchnschr., 1917, **54**, 283.
156. Wile, I. S., and Orgel, S. Z.: Med. J. and Rec., 1928, **127**, 431.
157. Wile, I. S.: Internat. Clinics, 1928, **111**, 145.

MISCELLANEOUS.

158. Chalmers, G. S.: New York Med. Rec., 1883, **24**, 390.
159. Down, L.: London Hosp. Rep., 1866, **3**, 259.
160. Newman, H. H.: Biol. Bull., 1928, **55**, 283.
161. Rook, C. W.: J. Am. Med. Assn., 1894, **22**, 382.
162. Summers, J. E.: Ann. Surg., 1915, **62**, 138.
163. White, C.: Proc. Roy. Soc. Med., 1912, **5**, Obst. Sec., 247.

ASTHMA DUE TO THE MAYFLY.

By Karl D. Figley, M.D.,
TOLEDO, OHIO.

Three years ago, a patient was encountered who attributed his seasonal attacks of asthma to the annual invasion of swarms of Mayflies from Lake Erie. Upon investigation, such proved to be the case. Since our attention was first called to this condition, we have discovered three additional cases. Nowhere, have we found in the literature instances given in which insects themselves were the direct inciting cause of asthma. For this reason, we report the cases to follow and give a short description of the life habits of the Mayfly, with an explanation of the manner by which its produces asthma in susceptible persons.

Case Reports. Case I.—Mr. W. H. T., aged thirty-seven years, who resides at Point Place which is on the west side of Maumee Bay, Lake Erie, was first seen on July 21, 1926. His complaint was of an asthmatic attack which had begun about July 1 and which had persisted almost continuously since. The patient stated that he formerly suffered from hay fever for some fifteen years. For the last three years, there had been no hay fever, but he had had asthma alone coincident with the annual invasion of the Mayflies from Lake Erie and lasting until they had disappeared. These annual invasions usually began about July 1 but sometimes occurred earlier. The patient further stated that he only obtained relief from his asthmatic paroxysms by going to the home of his sister in Toledo, a distance of several miles from the lake, where there were no Mayflies about.

Physical examination showed no abnormalities except the usual chest findings during an attack of bronchial asthma.

Cutaneous Tests. An extract was made from some dead Mayflies, using Coca's solution for the extracting fluid. By the scratch method, the patient gave a large positive reaction to this extract, the wheal measuring 2.8 cm. in diameter, with pseudopodia and a wide border of erythema. The control test was negative. Mild positive reactions were also obtained to short and giant ragweed pollens. It was noticeable that reactions to timothy, June grass and orchard grass were negative, these being the pollens prevalent in this vicinity during June and July.

Progress of Case. No attempt was made to desensitize the patient when he was first seen, as the swarming season for the Mayflies was nearly over. He reported again in June, 1927, with a recurrence of his asthma, having been free since August 1, 1926. He stated that his asthma began on June 17, shortly after a northeast wind had brought a swarm of Mayflies from the lake. Desensitization by means of gradually increasing doses of diluted extract was then commenced. The first injection consisted of 0.15 cc. of a 1 to 10,000 dilution, with no untoward reaction. These injections were repeated at intervals of five to seven days for the remainder of the summer. After a few doses had been given, the patient began to notice some relief and although the Mayflies swarmed at intervals until August 1, he obtained noticeable protection by the middle of July.

From September, 1927, injections of the extract were given at monthly intervals during the fall, winter and spring, the strength being gradually

increased so that a maximum dose of 0.3 cc. of a 1 to 30 solution was attained by June 1, 1928. The patient remained perfectly free from asthma during the summer of 1928 in spite of repeated exposure to the Mayflies.

CASE II.—Mrs. B. M. D., aged thirty-seven years, residing in East Toledo, first developed hay fever and asthma at the age of fifteen years and had had hay fever yearly since. In the spring of 1914, the family bought a cottage at Toledo Beach on the shore of Lake Erie. That June she had severe asthma lasting several weeks, coincident with the Mayfly invasion. She had no hay fever the remainder of the summer until late in the fall. Ever since 1914, patient had noticed that whenever she was exposed to these swarms of insects at the summer cottage she developed hay fever and asthma. For several years she has avoided going to the cottage during the swarming season and has had no symptoms until the middle of August.

By the scratch method, this patient gave marked positive reactions to short and giant ragweed. The reactions to June grass, timothy and orchard grass were negative. There was a huge positive reaction to Mayfly extract, measuring 3.5 cm. in diameter, with pseudopodia, erythema and itching.

No treatment with Mayfly extract was attempted as the patient avoided exposure by staying away from her cottage at the lake shore. Upon request, she returned for reëxamination in February, 1929, when it was found that she still gave marked positive skin reactions to the ragweeds and Mayfly extract but to no other substances.

CASE III.—The following case history was contributed through the courtesy of Dr. C. E. Price of Toledo. "E. M., male, aged twenty-seven years, seen only once during July, 1928; has had hay fever symptoms for the past four years. The first year, rather mildly. The symptoms have begun about the first of July and he has noted that they develop with the arrival of the Mayflies from Lake Erie, his home being on the lake shore. With the disappearance of the flies, his symptoms have ceased and he has no such symptoms throughout the remainder of the year. He is not subject to frequent colds. In 1928 and to a lesser extent in 1927, he noted some asthmatic symptoms. He stated that on his way to Toledo, when he got farther away from the lake, his symptoms began to improve and during his stay overnight in Toledo, he had very slight obstruction to breathing and much less sneezing.

"Examination by a rhinologist gave negative findings except for typical allergic appearance of nasal mucosa. Cutaneous skin reaction to Mayfly extract gave marked positive reaction, rated at 5+. Reactions to grass pollens prevalent at this time were negative."

CASE IV.—Mr. L. H., aged thirty-six years; residence Sandusky, Ohio. Since the age of six years, he has had annual attacks of nasal obstruction, coryza, itching of eyes and mild asthma, always associated with invasions of Mayflies, lasting from about July 1 until middle of August. He has had no symptoms at any other time of year, and has never been free from symptoms any year since the trouble began.

This patient stated that his symptoms are always worst when storms from the northeast blow across Sandusky Bay bringing with them large numbers of Mayflies. Direct contact of these flies with the skin of his neck and face causes huge hives.

The scratch test with a drop of Mayfly extract gave a large positive reaction measuring 2.3 cm. in diameter with pseudopodia, erythema and itching. All other tests were negative including grasses and ragweeds. This patient was seen for the first time quite recently and is now being desensitized to Mayflies.

The Mayflies (Ephemerida). Mayflies (lake-flies, shad-flies, June-flies, "Canadian soldiers") belong to the Order Ephemerida. They are found along the shores of lakes and large rivers in various parts of the world and are especially abundant in the Great Lakes region. The Mayfly larvæ because of their aquatic existence, are of great importance as fish food in fresh-water lakes and streams. So important are these insects from an economic standpoint that the Bureau of Fisheries has sponsored investigations of their distribution and life habits. The latest and best of these reports is a study by Needham[1] entitled, "Burrowing Mayflies of Our Large Lakes and Streams." This study contains a complete bibliography. A more extended description of the life habits of these insects may be secured from the texts by Comstock[2] and by Kellogg.[3]

The name of this order is from the Greek word Ephemeros, "lasting but a day." It was given to these insects on account of the shortness of their lives after reaching the adult state. This order includes only a single family, the Family Ephemeridæ. There are about 300 known species of Ephemeridæ of which some 85 occur in North America.

Prof. Clarence H. Kennedy[4] of the Ohio State University contributes the following information regarding our local species: "The common species at Toledo which come out of the lake in such great abundance is Hexagenia bilineata (Fig. 1). Just before this large one appears in such great numbers, a species slightly smaller with speckled wings appears, which is Ephemera (Fig. 2). The large species, Hexagenia, has a brown stripe along the front side of the wing. About a dozen other small species occur along the Lake Erie shore, but you seldom see these more than a dozen specimens at a time."

Life History. In its under-water form, the Mayfly exists as a tiny six-legged creature called a nymph (Fig. 3). It has delicate fringed gills along its sides, two or three long appendages on the end of the body, and strong jaws with which to burrow and chew (Fig. 4). It can both walk and swim and lives on the bottom of shallow lakes and streams, feeding on small particles of animal or vegetable matter. This nymph crawls about, feeds, grows and undergoes frequent moults. After about the ninth moult (there may be twenty moults in all) there appear on its thorax four little sacs which are the beginning of the wings. With each moult these grow larger until finally at the end of the immature life, the nymph splits open the cuticle along the back and after hardly a second's pause the winged Mayfly emerges. The life of the nymph is from one to three years, depending on the species.

Most of the Mayfly species go through another moulting after acquiring wings. After flying a short distance, the Mayfly alights and sheds its skin again, a thin layer coming off from all parts of its body—even from its wings. The stage between the first issuance

FIG. 1.—Adult male Mayfly, Hexagenia bilineata. (After Needham.)

FIG. 2.—Adult male Mayfly, Ephemera varia. (After Needham)

FIG. 3.—The nymph of Hexagenia bilineata; dorsal view. (After Needham.)

FIG. 4.—The nymph from the side. (After Needham.)

from the water with expanded wings and the final moulting is called the subimago stage and may last in various species from a few minutes to twenty-four hours.

About July first along the shores of Lake Erie, swarms of the adult Mayflies appear. They come in waves for the succeeding four to six weeks. Myriads of these insects and their shed skins may be seen clinging to the sides of buildings (Fig. 5), trees or on shrubbery near the lake shore. Sometimes the winds carry dense clouds of Mayflies far inland. Pavements are often made slippery by their dead bodies which may accumulate to a depth of several inches. Sometimes the great swarms fall to the waters surface and are finally cast up on the beach in thick windrows, miles long.

The flying dance is the most conspicuous event in the life of the fully-developed, winged Mayfly and indeed makes up nearly all of

FIG. 5.—Mayflies on side of building. (After Needham.)

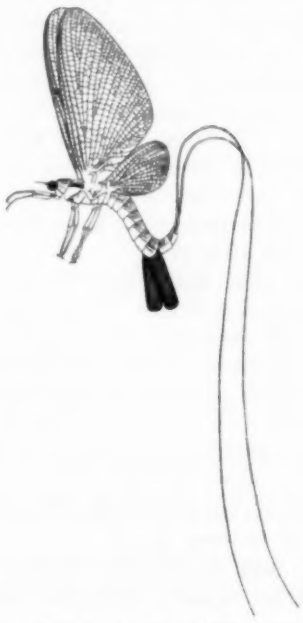


FIG. 6.—Adult female, hovering with egg packets extruding. (After Needham.)

it, for owing to the lack of suitable mouth parts with which to take food, the winged adult lives but a few hours. It has but one duty to perform in its brief life in the air: to reproduce its kind. In the early twilight, the fly comes forth full fledged, joins its thousands of issuing companions, mates, drops its masses of eggs (Fig. 6) onto the lakes surface and soon flutters and falls after the eggs. From each egg dropped on the water, hatches a nymph to perpetuate the species.

Discussion. When the patient described under Case I was first encountered, we were at a loss to account for the relation between the swarming of the Mayflies and this man's asthma. The Mayfly gives off no emanation. Its wings and body are formed of a chitinous material and the shaking of a large number of the dead insects in a glass jar, produced no dust. Furthermore, the dead insects when decomposed, are reduced to an oily mass which obviously cannot be wind-borne. It was only when we learned of the final moulting of the Mayfly after its emergence from the water and the shedding of its skin after the subimago stage that the mode of production of the asthmatic paroxysms was clear. This shed skin is very thin and delicate and upon close observation when the Mayflies are swarming, fragments of it may be seen adhering to walls, posts, trees etc., where it has been deposited. Particles of the shed skin are readily wind-borne and when one considers the millions of insects which take part in the annual Mayfly invasion, it is not difficult to obtain some comprehension of the amount of allergenic material given off by these insects. As had been described the Mayflies are piled up in long windrows on the lake beach and they accumulate by the ton along the streets of lakeside towns. These piles of decomposing insects give off a strong "fishy" odor, and their composition no doubt resembles that of fish because of their long aquatic existence. To those familiar with the ability of fish proteins to cause asthma in specifically sensitized individuals it will be readily understood how the shed skin of the Mayfly can be a potent cause of asthma in those who have become sensitized to it from long exposure, year after year.

It should be stated that since 1927 we have used the Mayfly extract routinely in our skin tests. In several hundred cases, the four above reported were the only ones to give definitely positive reactions. This we regard as further corroboration of the specific sensitization of these four patients to some substance in the shed pellicle of the Mayfly.

Summary. 1. Four cases of asthma due to Mayflies have been reported.

2. The asthma has been caused by the inhalation of minute particles of the shed pellicle of these insects.

3. One patient has been successfully treated both preseasonally and coseasonally with an extract made from dried Mayflies.

4. Use of Mayfly extract routinely in skin tests on several hundred patients has given positive reactions in only the four cases cited.

5. Attention is called to the widespread distribution of these insects in rivers and fresh-water lakes throughout the world, and the possibility of their being sensitizing agents.

REFERENCES.

1. Needham, James G.: Burrowing Mayflies of Our Larger Lakes and Streams, Bull. Bur. Fisheries, 1917–1918, **36**, Document No. 883, issued July 17, 1920.
2. Comstock: A Manual of the Study of Insects, Twelfth edition.
3. Kellogg, Vernon: American Insects, Henry Holt & Co., New York, Second edition, 1908.
4. Personal communication.

A CLINICOPHYSIOLOGIC STUDY OF THE PATHWAY OF PAIN IMPULSES IN CARDIAC DISEASE.

By George I. Swetlow, M.D., F.A.C.P.,
ASSISTANT PHYSICIAN, MANHATTAN STATE HOSPITAL FOR THE INSANE, WARD'S ISLAND, N. Y.

Introduction. In a former contribution,[1] a report was made on the clinical results obtained in the relief of cardiac pain by means of paravertebral alcohol block. Observations were then made as to the pathway that these pain impulses took from the heart to the spinal cord before passing into the spinothalamic tracts to be transported by these pain conveying tracts to the diencephalon. At that time the examinations made suggested that the pathway along which these pain impulses traveled from the *situs* of origin, the heart, was through the stellate ganglion as well as through those rami communicantes and spinal ganglia which were found to extend from the eighth cervical down to the sixth and seventh thoracic (C 8 to D 7), before they entered into the spinal cord to be conveyed *via* the spinothalamic tracts to the thalamus, as pain. In a recent article by Ionescu,[2] experimental observations were made on animals, which confirmed these previously observed clinical evidences, thus tending to confine the afferent sensory pathway from the heart to those rami communicantes and spinal ganglia found between the eighth cervical (C 8) and the seventh thoracic (D 7) ganglia. This paper is presented to correlate these previously made clinical findings with the subsequently independently-made observations on animals in order to establish more firmly the pathway for cardiac pain.

Anatomical Pathways of the Afferent Cardiac Nervous System. The following description presents the anatomy of the cardio-afferent nervous system:

The cardiac plexus is brought into contact with the sympathetic system through three cardiac nerves, that is, the superior, middle

and inferior cervical cardiac nerves. These nerves originate from the superior, middle and inferior cervical ganglia. The right superior cervical nerve enters the deep cardiac plexus and gives off a few branches to the anterior surface of the aorta. The left superior cervical cardiac nerve joins the superficial cardiac plexus. It is of importance to note that the superior cardiac nerve communicates freely with the middle cardiac nerve and with the superior cervical cardiac branch of the vagus. The middle cervical cardiac nerve arises from the middle cervical ganglion. Often this nerve and ganglion are entirely absent. Both the right and left middle cervical cardiac nerves end in the deep cardiac plexus. The middle cervical cardiac nerve anastomoses in the neck with the superior cervical cardiac nerve and the inferior laryngeal nerve of the vagus. The inferior cervical nerve arises from the inferior cervical ganglion and at times from the first thoracic ganglion. It anastomoses with the middle cervical cardiac nerve and the inferior cardiac nerve. The lowest cardiac nerve terminates in the deep cardiac plexus while the vagus nerve also ends in the deep cardiac plexus. The nerves of the heart are derived from the cardiac plexus. These nerves pass down along the aorta and are distributed to the auricles. From there they accompany the coronary arteries along the auriculoventricular groove thus forming the coronary plexus. From this plexus, branches are given off to the ventricles. The ascending aorta has nerve fibers which are in relationship through the rami communicantes with the first six spinal thoracic segments.

There is some question as to whether the afferent fibers of the inferior cardiac nerve pass to the fourth, fifth, sixth and seventh cervical nerves. There is evidence to the contrary. First, clinically, it is rare for pain to appear over the dermatomic segments supplied by the fourth, fifth, sixth and seventh cervical roots. Embryologically the evidence is also against this occurrence. Afferent fibers from the heart enter the upper cervical and thoracic segments which extend from the first to the seventh dorsal segments. Apparently, in the development, the fibers going to the lower cervical nerves are not developed from the inferior cardiac nerves. All three cardiac nerves convey motor impulses to the cardiac plexus. Ranson maintains that most or all of the constrictor fibers to the aorta and coronary vessels come through the superior cardiac nerve. The sensory afferent impulses from the middle and inferior cardiac nerves reach the spinal cord through the rami communicantes. They enter into the thoracic segments, extending from the first to the seventh segments. These sensory afferent fibers pass into the central nervous system by way of the rami communicantes into the upper thoracic segments. Hypothetical nerves, such as a special depressor nerve and the vertebral nerve and structures seen in comparative anatomic studies but not established for human beings, are omitted in this discussion.

Clinical Evidence Concerning the Pathway of Cardiac Pain as Ascertained by the Subjective Radiation Complained of by the Patients. Irrespective of the place of origin of those painful stimuli which give rise to cardiac pain, and of the nerves through which they pass, these impulses must ultimately pass into the spinal cord or brain stem to travel by way of the spinothalamic tracts in the spinal cord to the thalamus and thus ultimately reach the sphere of consciousness. Before entering the spinal cord however, these pain impulses, as with any pain impulses, must first enter the dorsal-root ganglia so as to give rise to the phenomenon of referred pain. It is upon these basic physiologic principles that these subjective pain areas, as complained of by the patients are explained. Of further interest, are the observations, that the areas complained of are parts of the body surface relegated in nearly all of the cases to dermatomic segments that are supplied by those spinal nerves found between the eighth cervical and seventh thoracic segments. In a careful examination of the histories personally taken, as well as a perusal of the literature of many cases of pain due to angina pectoris, coronary disease and aortalgia, one is quite forcibly struck with the fact that the radiation of pain is relegated quite consistently to those areas of the body supplied by the eighth cervical down to the sixth or seventh dorsal (C 8 to D 7) nerves. These observations also revealed that any part or all of the chest may be subjectively referred to as the seat of the pain. Although it is true that at times the patients complain of pain in the back of the head (C 1-2) or in the ear (C 2) and at times in the lower jaw (trigeminal), yet it is worthy to note, that these two former sites are of rare occurrence while the last site is indeed a curiosity. A complaint of pain along the outside of the arm, which is supplied by the fourth, fifth, sixth and seventh cervical nerves is of such rare occurrence, that its actual existence is greatly to be doubted. In fact, anatomically, it is quite likely that no afferent sensory fibers of the inferior cardiac nerve pass through these four latter cervical nerves. Embryological studies also seem to support this conclusion. Therefore, from a clinical point of view as ascertained by the subjective complaints of the patients, we can logically say, that the impulses, which produced pain passed through dorsal root ganglia which supplied those dermatomic segments innervated by nerves emerging from between the eighth cervical and seventh dorsal spinal segments.

Clinical Evidence Concerning the Pathway of Cardiac Pain as Ascertained by the Neurologic Examination of the Patients. (Head Zones.) As stated, all sensory impulses, which are conveyed by nerve fibers from an organ, must first enter into dorsal root ganglia before entering the spinal cord to be conveyed by the spinothalamic tracts to the sensorium. The spinothalamic fibers transmitting

these stimuli arborize about cells in the dorsal root ganglia known as Dogiel cells. The constant bombardment of these somæ by discharges coming from a diseased organ produce in these cells a state of hyperirritability. When a sensitive dermatome, which is supplied by such an irritable cell, is roused by any physical agent, that is, pin prick, heat, cold—a painful response ensues. We thus see that this method of investigation is of great value in ferreting out those ganglia which are the recipients of the continuous stream of painful impulses from the diseased organ. Simply stated, this method reveals the pathway along which the painful influences are traversing so as to enter the spinal cord. Based upon these neurophysiologic facts, careful epicritic and protopathic tests were performed. In the 8 cases originally reported and 12 cases to be reported, definite sensory changes were observed over the skin. In all cases the protopathic skin tests clearly gave proof of the hypersensitiveness of the skin. Those zones of hyperirritability were limited to areas of the skin supplied by those peripheral nerves which emerge from between the eighth cervical down to the seventh thoracic spinal segments. Again, it is of value to note, that the neurologic examination failed to elicit Head Zones over the back of the head (C 1–2) or over the lower jaw (trigeminal nerve). The investigation also failed to reveal any hypersensitiveness of the skin to these tests over the radial aspect of the upper extremities (C 4–5–6–7).

This method, therefore, also seems logically to suggest that the discharges of pain from the heart pass *via* those sympathetic fibers and dorsal root ganglia that are emerging between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments.

Operative Evidences as to the Pathway of Cardiac Pain as Ascertained from the Various Procedures Performed. In reviewing the various operative measures instituted for the amelioration of the severe pain incident to cardiac disease, data were also elicited which clearly indicated what was not the pathway of pain from the heart. Nevertheless, these failures in the several surgical attempts to relieve the pain are of invaluable importance in indicating the correct pathways. Since the original suggestion of cervical sympathectomy by François Franck and the first actual surgical interference for the relief of angina pectoris by Jonnesco, of Bucharest, in 1916,[3] surgeons have attempted to relieve the agonizing pain incident to the cardiovascular disturbance. That the surgical attempts are based on insufficient and inadequate anatomic, physiologic and pathologic evidence is amply borne out by the great variety of surgical procedures attempted. The various surgical operations will be reviewed and discussed briefly, so that a clearer understanding may be obtained as to the significance of the information elicited, thus aiding in the disclosure of the correct pathway for cardiac pain.

1. Method of Jonnesco. By this method the entire cervical chain, along with the first thoracic ganglion, was extirpated (Fig. 1). Danielopolu objected to this method. He contended that this operation severed the vasomotor fibers to the coronary arteries as well as the vasoconstrictor fibers to the lung. These objections were answered by Jonnesco in a recent article. He asserted that physiologists, supported by extensive experimentation, are of the opinion that the sympathetics are vasoconstrictors. Hence the removal of the sympathetics does not impair the efficiency of the coronaries but, in fact, augments it.

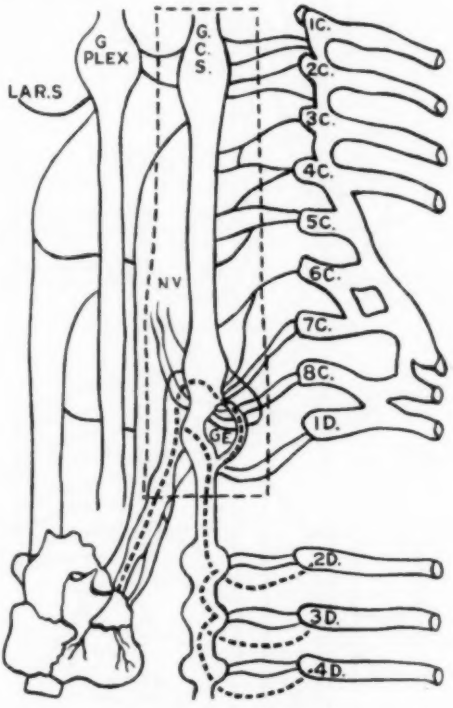


FIG. 1.—(After Danielopolu.)

2. Method of Danielopolu and Hristide.[4] These operators sectioned the cervical sympathetic cord on the left side above the stellate ganglion (Fig. 2). Along with this section, the spinal ganglia of the spinal nerves on the left side were injected with alcohol. At that time the operators were not ready as yet to report the value of this method.

3. Method of Danielopolu. (A) On January 1, 1924, this surgeon reported that Gino Pieri of Bellino was the first to follow the operator's new method. He sectioned the cervical sympathetic

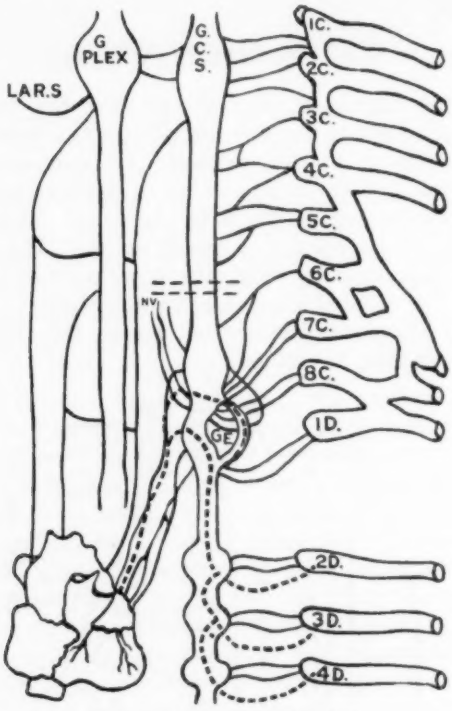


Fig. 2.—(After Danielopolu.)

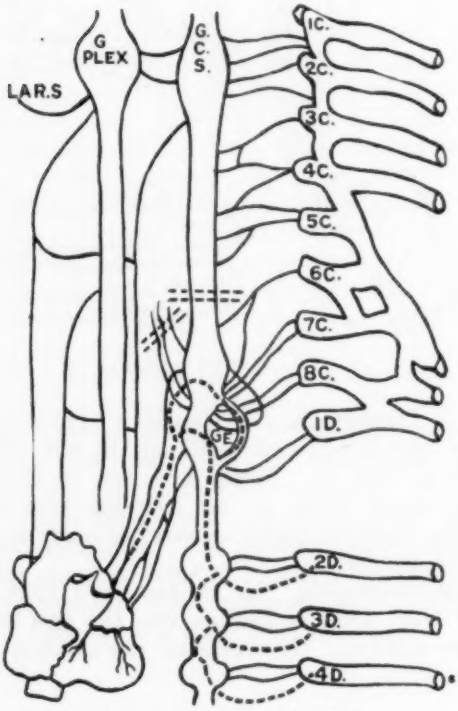


Fig. 3.—(After Danielopolu.)

chain above the stellate ganglion, together with the vertebral nerve, as well as a nerve which joins the superior cervical ganglion to the cranial nerves (Fig. 3). The immediate results were good. No report as to the condition of the patient at a later date was given. (B) In October, 1924, Danielopolu reported resection of the sympathetic cervical chain without removal of the inferior cervical ganglion and the first thoracic ganglion (Fig. 4). In addition he sectioned the vertebral nerve and the branches of the vagus, which were about to enter the thorax. (C) In a less complete operation the

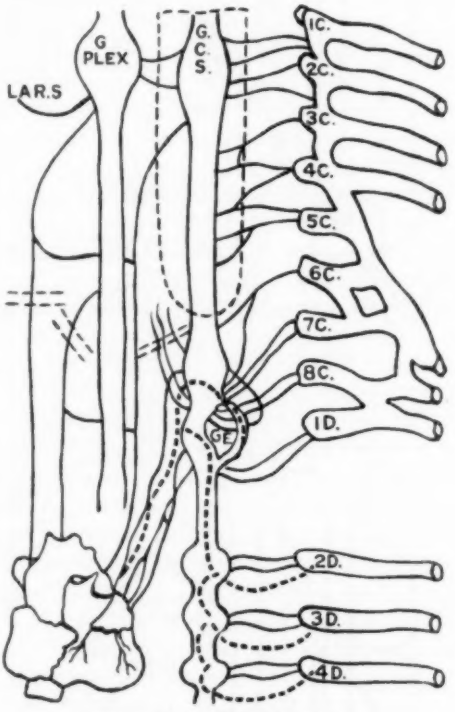


FIG. 4—(After Danielopolu.)

superior and middle cervical ganglia were extirpated on one or both sides (Fig. 5). In January, 1925, Lilienthal[5] reported three such cases with good results. (D) In February, 1925, the following operation was performed by Danielopolu: the cervical sympathetic chain was resected. The inferior cervical ganglia, as well as the first thoracic ganglia, were left intact. The vertebral nerve was sectioned. All branches leaving the vagus to enter the thorax were severed. The rami communicantes, which joined the inferior cervical ganglion and the first thoracic ganglion to the last pair of cervical nerves, were severed (Fig. 6). In addition to the above

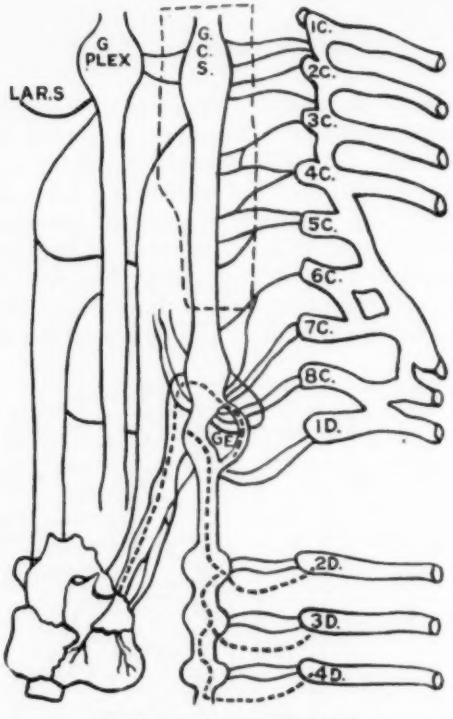


FIG. 5.—(After Danielopolu.)

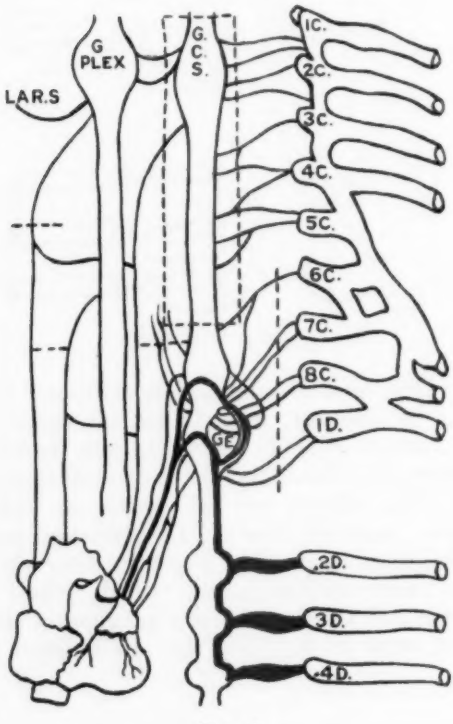


FIG. 6

operations, Eppinger and Hoffer sectioned the so-called depressor nerve, while Coffey and Brown severed the cervical sympathetics, together with the superior cardiac nerve on the left side. Hoffer in four cases of angina pectoris dissected the vagus nerve without influencing the severity of the pain.

The résumé of these various operations shows quite suggestively, that if pain impulses do pass through the middle, superior cervical ganglia and vagus they do so in a very minor degree. These observations are quite supported by the animal experimentations to be later discussed as well as by the results obtained by the paravertebral alcohol nerve block.

Evidence as to the Pathway of Cardiac Pain Elicited by Means of the Paravertebral Block. In a former contribution, a report of 8 cases suffering from cardiac pain was made showing the results obtained by destroying the rami communicantes and dorsal-root ganglia conveying impulses of pain from the heart. In addition to the former report, data, not as yet reported, will be incorporated here as well as 12 additional cases treated by the writer. In these 12 cases gratifying results were obtained in all but 2 cases. In a recent paper from the Massachusetts General Hospital[6] 5 additional cases were reported in great detail in which the alcohol paravertebral alcohol block was used with admirable results. Mandl[7] also reported 16 cases treated by this method with excellent results. This discussion, therefore, is based on a total of 41 cases, treated independently by three different operators. This method is of invaluable aid in the study of the route taken by these impulses which incite the perception of cardiac pain, in that we destroy nerve fibers and then observe what ensues to the complaint of pain as personally expressed by those treated. The following theoretical principles are of value in understanding the paravertebral alcohol block as a method in studying the course of cardiac pain. As previously stated, the cardiac pain was referred subjectively to the surface of the body supplied by part or all of the nerves coming forth from between the eighth cervical down to the seventh thoracic nerves (C 8 to D 7), and again, as formerly set forth, these very same skin segments were the ones which were sensitive to skin tests. The conclusion was quite evident, that if these irritable ganglia or sympathetic fibers, which came to the ganglia from the heart loaded with pain impulses were destroyed, and if pain, as a result of the destruction, disappeared, the pathway of cardiac pain to a great extent would be solved. In light of the fact that an 80 per cent solution of alcohol destroys myelin and since the afferent sympathetic fibers are finely myelinated, a paravertebral alcohol block was performed, injecting each of the irritated ganglia. As a result of the injection into the nerve tissue, a typical Wallerian degeneration was produced. In all of the cases, the paravertebral injections were confined to those ganglia found between the eighth cervical and seventh thoracic (C 8 to D 7) spinal segments. The

analysis of the 41 cases showed that those treated were mostly far-advanced patients of heart disease, who suffered because of the persistent agonizing pain—that they all received a paravertebral alcohol injection into some or all of the dorsal root ganglia and rami communicantes which extended between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments—that, except for 4 cases, they were all relieved to a marked degree. Since the cardiac pain was relieved by the destruction by alcohol of the irritated ganglia found between the eighth cervical and seventh thoracic, we can reasonably say that the impulses of pain were intercepted by the alcoholic destruction of the nerves before they were able to enter the spinal cord, and since only nerves found between the eighth cervical and seventh thoracic were so destroyed, the conclusion naturally follows, that the pathway of pain is through those rami communicantes and dorsal-root ganglia found between the eighth cervical and seventh dorsal (C 8 to D 7) spinal segments.

Evidence Elicited by Means of Animal Experimentation as to the Pathway for Cardiac Pain. In a recent paper by D. Ionescu, experimental observations were made upon dogs and cats as to the course taken by discharges capable of producing cardiac pain. His experiences support the same conclusions as were arrived at through our clinical studies upon human beings. The following is a résumé of the method used by the experimentor and the interpretation of the results as made by him. The experiment may be divided into four steps.

Step I. Upon the pericardium or epicardium being pinched or pulled, or on the application of a 10 per cent solution of ammonium or barium chlorid to the left ventricle or on making a similar chemical application to the adventitia of the left coronary artery or aorta, definite manifestations of pain reactions upon the part of the animals were seen, that is, marked movements of defence, increased respirations, rise in the blood pressure.

Step II. The next step of the experiment was to sever on the left side the rami communicantes of the eighth cervical and the first thoracic (C 8 to D1) as well as the rami communicantes of the thoracic sympathetic chain down to the sixth ganglion. The first thoracic ganglion was not removed so as to permit its continuity with the cervical sympathetic chain and the vertebral nerve. With this section accomplished, there remained the following routes for the transmission of pain impulses from the left heart—the vagus with its depressor branch, the superior cardiac nerve, the cervical part of the sympathetic ganglionated chain. the vertebral nerve. Again the epicardium and pericardium, the left coronary artery and aorta were stimulated as was done in Step I and none of the reactions of pain as already described appeared in the animal. However, stimulating the right ventricle, a display of pain reactions were again elicited though mild in nature. No evidences of pain resulted at

all when the aorta was stimulated, even though the nerve structures were preserved on the right side.

Step III. The next step was to resect on the right side the rami communicantes, which extended from the eighth cervical down to the sixth thoracic (C 8 to D 6). The application of the physical and chemical stimuli to the left or right ventricle, coronary artery or aorta roused no pain manifestations. This absence of pain is observed even though the vagus nerve, the depressor nerve, the superior cardiac nerve, the vertebral nerve and the cervical sympathetic chain are left unmolested.

Step IV. In other experiments as carried out in man, the same operator stimulated the cranial end of the sympathetic chain but no pain was produced.

Additional evidence was brought by Schittenhelm and Kappis to the effect, that the cervical sympathetic chain does not transport pain discharges from the heart and the aorta. They observed attack of angina pectoris during an operation. They immediately injected novocain into the trunk of the cervical sympathetic chain with no relief ensuing, while upon injecting the stellate ganglion, there was at once a suppression of the pain. In an earlier paper, D. Ionescu showed that the electrical stimulation of the cranial end of the vagus nerve as well as the depressor nerve or vertebral nerve, when found in man, incited no pain reactions. Hoffer noticed in 4 cases of angina pectoris no influence upon the pain by severing the vagi. D. Ionescu pinched and pulled upon the vagus nerve without inducing pain evidences in the animals experimented upon. The experiments of Ionescu, together with the work of Hoffer, Schittenhelm and Kappis lead to the conclusion, that the impulses of pain pass from the heart through the stellate ganglion (C 8 and D 1) as well as those rami communicantes that are found between the eighth cervical and sixth thoracic spinal segments.

Case Reports. The first three cases are from the Medical Division, Montefiore Hospital, service of Dr. B. S. Oppenheimer.

Case I.—The patient, R. C., a young female, aged twenty years, suffered from aortitis and aortic insufficiency caused by congenital syphilis. Her complaints of pain began April, 1923. In the very beginning the pain appeared over the precordium. In a few months the discomfort extended to the left shoulder blade, down the left arm and the back of the chest on the left side. The arm pain was sticking and constricting in character and was especially bad during the night. After April 17, 1924, the pain became much more severe. The attacks consisted of paroxysms of severe sticking pains lasting a few minutes and leaving in their wake a dull ache over the same area. These paroxysms were brought on with only slight exercise, and, as a result, greatly curtailed her physical activities.

She received a course of salvarsan and mercury salicylate (which was completed October 2, 1924), potassium iodid (which was discontinued several months ago), and a series of injections of Bismogenol. Following this series of treatments, she was slightly more comfortable, but the pain still persisted.

A paravertebral alcoholic injection was performed April 23, 1925. After the injection into the fourth, fifth, sixth and seventh dorsal roots on the left side, the patient was almost completely relieved of pain and in addition was able to carry on increased physical activity to exhaustion without attacks of pain. For example, before the injection of alcohol she was unable to walk more than one block without developing sharp, excruciating, sticking pain over the left chest anteriorly and posteriorly, with radiation to the left arm as far down as the hand. The pain was so severe that she was forced to stop, the distress lasting two to three minutes at a time. At present, she is able to walk from five to ten blocks, and, although she at times develops pain, she asserts that it is so mild and fleeting that she pays but little attention to it. Previous to the alcoholic injection she found that on attempting to practise on the piano for more than ten to fifteen minutes, she would be forced to stop because of the agonizing pain. Now she is able to play for at least one hour and at times more. Only occasionally has she a short fleeting pain over the left precordium. The following are the sensory changes observed before and after the injection.

April 22, 1925. Before the injection (Fig. 8).

A. Epicritic sensibilities. (1) Hyperesthesia to light touch with cotton wool extended from the third to the seventh dorsal nerves on the left side anteriorly and posteriorly. (2) She was able to discriminate temperatures ranging between 20 and 38° C. over the same region. (3) Cutaneous localization was well performed.

B. Protopathic sensibilities. (1) A zone of hyperalgesia to pin prick extended from the third to the seventh dorsal nerves on the left side. (2) A marked hyperthermalgesia was observed on the left side of the chest to temperatures above 45° and below 20° C., when compared to the right side. She was able to recognize these extreme differences in degrees on the left side.

June 1, 1925, thirty-nine days after the injection.

A. Epicritic sensibilities. (1) A zone of hypesthesia to light touch with cotton wool extended from the third to the seventh dorsal nerves on the left side. In fact, she hardly perceived the stroke of the cotton wool. (2) She was definitely unable to discriminate over the injected segments, temperatures ranging from 26 to 38° C. (3) Cutaneous localization was greatly impaired.

B. Protopathic sensibilities. (1) An area of hypalgesia to pin prick extended from the third to the seventh dorsal nerves on the left side. (2) A marked hypothermalgesia was found on the left side extending from the third to the seventh dorsal nerves, when compared with the right side. There was noticed great impairment in her ability to discriminate between extremes of temperature on the left side, that is, between 20° and above 45° C.

Case Summary. (1) Before injection a zone of dermatomic irritability extended from the third to the seventh dorsal nerves on the left side. Sensory examination thirty-nine days after the injection showed that the nerve conductivity was greatly reduced. (2) She had been free from pain for four months when she was discharged from the hospital. On October 25, 1925, approximately twenty-six weeks later, we received a letter from her in which she reported that she is able to walk as far as a mile without the appearance of pain.

Case II.—The patient, F. S., a male, aged sixty-three years, suffered from angina pectoris, due to coronary disease. Fifteen months before admission, he complained for the first time of a severe, boring, retrosternal pain which penetrated anteroposteriorly. Frequently he observed that the pain was burning in nature, simulating "a feeling of hot sand." At times it was so excruciating as to induce crying. The pain would persist for twenty to twenty-five minutes, requiring morphin for its control. He

could walk no further than three blocks at a time, for, if he did, agonizing pain ensued. Twice this necessitated his being taken from the street to a hospital in an ambulance. Inhalation of amyl nitrite often relieved his attacks. Several months ago he felt for the first time slight burning paresthesia down the left upper extremity.

On June 25, 1925, he received a paravertebral injection of alcohol into the third, fourth, fifth and seventh intercostal nerves on the left side. Five cubic centimeters of 80 per cent alcohol solution were used in each dorsal root. Following this form of treatment the pains were completely relieved within twenty-four hours. There was practically no limit to his ability to walk. He was up and about most of the day, doing errands in the hospital, and he definitely asserted that he was relieved of his pain. Nevertheless, shortness of breath, when he exerted himself unduly, was a very prominent symptom. A sensory examination was done before and after the injection.

June 23, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to light stroking with cotton wool was found over the skin supplied by the second to the eighth dorsal nerves on the left side both anteriorly and posteriorly. (2) No disturbance was observed in his ability to discriminate temperatures ranging between 20 and 38° C. He had no difficulty in locating areas lightly touched.

B. Protopathic sensibilities. (1) An area of skin hyperalgesia to pin prick extended from the second to the eighth dorsal nerves on the left side. (2) An extreme hyperthermalgesia was present on the left side when compared with the right side. He was able to distinguish these extremes of temperature on the left side.

March 3, 1926, three hundred and thirteen days after injection.

A. Epicritic sensibilities. (1) When stroked lightly with cotton wool over the dermatomic segments supplied by the injected nerves, the patient hardly perceived being touched. (2) He was unable to discriminate temperatures ranging between 20 and 38° C. (3) Cutaneous localization was completely lost.

B. Protopathic sensibilities. (1) The patient observed that he could not feel the pricking of a pin over the areas of the skin supplied by the injected nerves. He experienced a peculiar dysesthesia, as he put it, "dull and frozen," when a pin was drawn across the skin. (2) His inability to discriminate the extremes of temperature was quite marked. There was, in fact, an almost complete analgesia.

Case Summary. (1) Before injection, a dermatomic zone of irritability was delineated. This extended on the left side over the skin supplied by the second to the eighth dorsal nerves. Three hundred and thirteen days after the injection, a sensory examination indicated that the nerve conductivity was greatly decreased. (2) He was completely relieved of all pain for a period of four months when it again appeared. He was reinjected, this time blocking the first, second, third and fourth dorsal-root ganglia and rami communicantes. Before the second injection the level of root hyperirritability was from the first to the third dorsal-root segments. Following the injection signs of diminished conductivity were noted. He is now again comfortable and free from all pain. He complains, however, of a pressing sensation over his shoulders when he attempts to rise from a sitting position, as well as of retrosternal pressure. He has now been relieved for a little more than ten months.

Case III.—This patient, Y. S., a female, aged eighteen years, suffered from mitral stenosis and insufficiency, together with cardiac decompensation. Fifteen months before admission she developed precordial pain for the first time. She described it as sticking in character lasting from a few

minutes to as long as an hour. At times the attacks of pain would appear during the night, awakening her from sleep. She complained that with the sticking pain there was a burning sensation in the skin. These attacks would appear for a few successive days and then disappear, only to reappear. For four months preceding the treatment, however, the pain had been persistent, always more or less severe. During the ten days before injection the agony was especially disturbing, being both sticking and constricting in type, with no remission either by day or night. The pain was particularly severe in the left interscapular region, preventing her from reclining on her back. On June 25, 1925, 4 cc. of a 60 per cent alcohol solution were injected into the third, fifth, seventh and ninth dorsal roots. After the injection she experienced precordial pain only occasionally and that which she did feel was slight and fleeting in character. She was able to recline on her back without pain or discomfort over the precordium. Within one week of the injection she observed a peculiar itching paresthesia over the site of the injection. On scratching it she noted that there was very little sensation induced on rubbing the skin.

The following is a summary of the sensory findings before and after the injection.

June 23, 1925, before the injection.

A. Epicritic sensibilities. (1) The dermatomic skin areas extending from the third to the eighth dorsal nerves on the left side both anteriorly and posteriorly showed a marked hyperesthesia. She noticed that light stroking with cotton wool induced an unpleasant scratching sensation. (2) Her ability to discriminate temperatures varying between 20 and 38° C. was normal. (3) Cutaneous localization was well performed.

B. Protopathic sensibilities. (1) A dermatomic zone of hyperalgesia extended from the third to the eighth dorsal nerves on the left side. (2) In the same dermatomic zone hyperthermalgesia was observed when compared with the right side. Temperatures below 20° and above 45° C. were used. There was no disturbance in her ability to recognize extreme temperatures on the left side.

September 11, 1925, seventy-eight days after the injection.

A. Epicritic sensibilities. (1) There was no disturbance in her ability to feel the light touch of cotton wool. (2) There was no disturbance in her ability to discriminate temperatures ranging between 20° and 30° C. (3) Cutaneous sensibility was found to be unimpaired.

B. Protopathic sensibilities. (1) Her reaction to pin prick on the left side was only slightly below normal. (2) Her ability to discriminate on the left side between extremes of temperature, that is, below 20° and above 45° C., was greatly impaired. When compared with the right side there was a definite hypothermalgesia.

Case Summary. (1) This patient was injected with a weaker alcohol solution, that is, 60 per cent. (2) The sensory findings after the injection showed the conductivity of dorsal nerves to be only slightly decreased as compared with the previous 2 cases in which an 80 per cent solution was injected. (3) She was free from all pain for fourteen weeks, finally died from cardiac decompensation.

Case IV.—The following patient is from the Neurological Division, Montefiore, Dr. S. P. Goodhart, chief of Division.

The patient, J. W., a male aged sixty-one years, suffering from angina pectoris associated with coronary disease and cerebral thrombosis, has for the past four years been complaining bitterly of precordial pain. At first the distress was brought on by walking two blocks, this causing such pain that he had to pause to rest. As time passed, he observed that walking even much shorter distances induced pain. He described this pain as stick-

ing, tearing, and at times constricting in character. These attacks would appear two or three times daily, each lasting from twenty to thirty minutes. For the past eighteen months he has been unable to walk more than twenty yards because of the induced agony. Every morning at about two o'clock he was awakened by severe precordial pain persisting from thirty minutes to an hour. He sat up in bed grasping his precordium. Occasionally he had a fear of impending death.

On June 12, 1925, a paravertebral alcoholic injection was performed. A very interesting phenomenon occurred while the patient was on the operating table. He suddenly started to groan with pain which was localized to the precordium. Accompanying this excruciating agony he became cyanotic. While in the throes of this anguish, 5 cc. of 1 per cent novocain solution were introduced paravertebrally into the first and second dorsal nerves. Within thirty seconds pain had completely ceased. Five minutes later 5 cc. of an 80 per cent solution of alcohol were introduced into each of the two dorsal nerves. The next day he walked 150 yards as fast as he could, and although he became alarmingly cyanotic and dyspneic, he asserted definitely that he had no pain. Since the treatment, he has been able to walk about comfortably with almost complete absence of precordial pain. He has had no further attacks of nocturnal pain.

Sensory findings June 11, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hypesthesia extended over the entire left side of the chest both anteriorly and posteriorly. (2) He had great difficulty in discriminating differences in fine degrees of temperature on the left side, both anteriorly and posteriorly. (3) Cutaneous localization was definitely impaired over the entire left side.

B. Protopathic sensibilities. (1) An area of hyperalgesia extended over the skin segments supplied by the first and second intercostal nerves on the left side. (2) A zone of hyperthermalgesia was observed on the left side over the first and second intercostal spaces. He found no difficulty in discriminating between extremes of temperature over the hyperirritable zones.

Case Summary. (1) Because of attacks of angina pectoris, the chest of a patient suffering from thrombotic processes, both in his interbrain as well as in the coronary arteries, was examined by sensory tests, which revealed disturbances in the afferent systems conveying impulses to the thalamus. Nevertheless, a zone of hyperalgesia was found over the skin areas supplied by the first and second intercostal nerves on the left side. (2) Because of signs pointing to a progression of the thrombotic process in his thalamus, it became quite evident that little information would be obtained by comparing the sensory examination of the chest before the injection with that after the injection. (3) No ill effects or complications of any kind following the injections have been observed. (4) He has now been relieved for approximately eight months.

Case V.—This patient, N. B., a male, aged sixty-five years, suffering from angina pectoris, due to coronary-artery disease, has complained of pain over the heart for a period of two years. The pain was chiefly located over the precordium and radiated down the left upper extremity and was described as constricting in nature and at other times as sticking in type. Often the pain was boring, seeming to penetrate anteroposteriorly. The attacks often occurred two or three times daily. Almost every night about two o'clock he would be awakened by a terrific pain over the precordium, accompanied by a sense of suffocation and a fear of impending death. Venesection was resorted to several times. Morphia relieved him, but amyl nitrite was of little avail. Physical examination showed a greatly enlarged heart with a marked dilatation of the aorta.

A paravertebral injection of alcohol was made into the second, third, fourth and fifth dorsal roots, which relieved him of further attacks, both

during the day as well as during the night. Shortness of breath still persisted upon excretion. Since the injection he has had several attacks of pulmonary edema with absence of pain. Before the treatment these attacks were always accompanied by severe, agonizing pain. Nine weeks later, during which time there was no pain, he suddenly died of pulmonary edema.

Sensory examination before and after injection showed the following:

September 15, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to cotton wool was found over the skin supplied by the first to the sixth intercostal nerves on the left side. (2) There was no disturbance noted in his ability to discriminate temperatures ranging between 20 and 38° C. (3) Cutaneous localization was well performed.

B. Protopathic sensibilities. (1) A zone of hyperalgesia extended over the skin supplied by the first to the sixth intercostal nerves on the left side. (2) There was noted a greatly increased reaction on the left side to temperature below 20° and above 45° C. He had no difficulty in recognizing these extremes of temperature on the left side.

November 15, 1925. Sixty days after the injection.

A. Epicritic sensibilities. (1) There was observed a marked hypesthesia which extended over the skin on the left side supplied by the first to the sixth intercostal nerves, respectively. In fact, he hardly perceived the stroking of the cotton wool over his skin. (2) He was completely unable to discriminate fine differences in temperature, that is, between 20 and 38° C. (3) Cutaneous localization was greatly impaired.

B. Protopathic sensibilities. (1) A zone of hypalgesia practically approaching analgesia extended over the skin segments supplied by the first to the sixth intercostal nerves. (2) A marked disturbance in his ability to discriminate between extremes of temperature, that is, below 20° and above 45° C. on the left side was noted. When the affected area was compared with the right side a definite hypothermalgesia was noted to exist over the former.

Case Summary. (1) Before the injection of alcohol a zone of hyperirritability existed over the skin dermatomes supplied by the first to the sixth intercostal nerves. Sixty-one days after the injection the conducting function of the intercostal nerves was greatly curtailed. (2) There was no return of pain in spite of the continuance of his attacks of pulmonary edema. On November 19, 1925, he died suddenly during one of these attacks. He was relieved for a period of nine weeks.

Case VI.—Patient, W. H., male, aged seventy-two years, is suffering from angina pectoris due to coronary disease. He was first seen by me December 4, 1925. His attacks of pain began six or seven years before. He described the pain as vise-like and sticking in character. The pain would begin in the precordium and radiate down the left arm. During the last two years, his condition became definitely worse. During the night, he was forced to sit up in bed because of the sudden pain. These nocturnal attacks became so frequent that he would experience this extreme discomfort three and four times nightly. He would remain absolutely quiet and fixed during the attack and felt as though he were about to die. The pain would last from fifteen minutes to an hour. For the past year his attacks would come on consistently, after eating even light meals or after walking a half to one block.

Physical examination showed a moderately enlarged heart with a marked widening of the aorta. A soft systolic murmur was heard at the apex, which was transmitted to the axilla. The heart sounds were of poor quality.

A paravertebral alcoholic injection was made into the first, second, third, fourth and fifth dorsal ganglia. His course twelve weeks after the injection is

as follows: He is able at present to walk twelve blocks without stopping, and there is no pain after this exertion. As was previously observed, the greatest distance he could walk before the injection was a half to one block. His appetite at present is excellent. Before the alcohol injection, the ingestion of even a little milk or cereal would initiate excruciating pain across the chest and down both arms. He would be forced to rise and stand absolutely at rest for as long as one hour before the attack would pass. At present he eats everything, meats, chicken, greasy foods, and so forth. He eats heartily and frequently with no pain. As a result of his increased diet, his general condition has improved. He has gained weight and his muscular tone, as evidenced by his quicker and firmer movements, has increased. The attacks, which occurred three to four times nightly have completely disappeared. Occasionally, during the day he has a sharp, fleeting pain over the precordium. The blood pressure before the injection was systolic 145 mm. and diastolic 85 mm. At present, the systolic pressure is 160 mm. and the diastolic 85 mm.

Sensory examination before and after the injection showed the following:

December 1, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to cotton wool was found over the dermatomes supplied by the first to the fifth intercostal nerves on the left side. (2) There was observed no disturbance in his ability to differentiate fine gradations of temperature. (3) There was no disturbance in cutaneous localization.

B. Protopathic sensibilities. (1) A zone of analgesia was found to extend posteriorly over the skin segments supplied by the first to the fifth intercostal nerves. (2) A similar zone of diminished sensitiveness to extremes of temperature was noted over the same areas.

Case Summary. (1) Before injection a zone of dermatomic irritability extended over the skin segments supplied by the first to the fifth dorsal nerves. Fifty-five days following the injections, signs of marked diminution of nerve conduction were observed. (2) Up to the date of this report, a period of twelve weeks, the patient suffering greatly from angina pectoris has been relieved of his pain. (3) The relief was accompanied by general physical improvement of the patient.

Case VII.—Patient, G. F., a female, aged sixty years, suffered from angina pectoris secondary to extreme coronary disease. She was referred to us by her son-in-law, a prominent physician in New York, who had observed her constantly for a long time. The following is a letter received from the doctor who gives the history briefly:

"The attacks of pain which Mrs. F. had were paroxysmal in character. The frequency of these attacks was variable, sometimes two and three times a day; toward the end they were almost continuous. The initial attack occurred about three years before, but at that time it was associated with hypertension and usually occurred upon exertion, particularly upon walking in the open.

"Physical examination at the time when you performed the operation was as follows: The heart was considerably enlarged, its action was variable, sometimes perfectly regular, at other times there appeared many extrasystoles. The musculature seemed poor and there were no adventitious sounds. The blood pressure varied between 130 and 140 mm. systolic and between 80 and 90 mm. diastolic. Originally the blood pressure was in excess of 200 mm.

"The condition at the time of exitus I cannot give you in detail. Following the operation, the patient's attacks changed from painful to nonpainful ones and for twelve hours preceding exitus, her breathing was regular,

heart action good, pulse full, rate about 100. The blood pressure was not taken. The exitus was sudden, so that the desired observations were not made. Signs of pulmonary edema appeared in the last moments but death was cardiac in origin."

The condition of this patient before injection was extremely poor. She was in great distress from pain and required constant hypodermic injections of morphin. In fact, her condition was so poor, that the inadvisability of carrying out the therapeutic measure was seriously considered. The distress was so great, however, that the procedure was tried to give her her only chance for relief. For five days following the injection she had no pain. She could eat better and was able to recline flat on her back with only one pillow under her head, whereas before she required three to four pillows. Her color became good, and she was permitted to sit in a chair. On the sixth day, she died suddenly. As observed by her physician, there was no pain during this sudden attack.

A preliminary sensory examination was done before the injection. A zone of hyperirritability was found to extend over the skin supplied by the first to the ninth dorsal nerves on the left side. These nerves were blocked. Each root was injected with 7 cc. of an 85 per cent solution of alcohol. Following the injection, sensory examination showed these roots to be destroyed, as they carried few peripheral sensory impulses.

Case Summary. (1) An old woman, suffering from severe cardiac pain due to advanced coronary disease, was injected with alcohol paravertebrally. (2) Her condition was so poor that the inadvisability of injecting was seriously considered. (3) Following the injection she was completely relieved of pain. During this period of freedom from pain she died suddenly.

Case VIII.—This patient, M. A., male, aged sixty-two years, was first seen by me October 26, 1925. His complaints of pain over the precordium began approximately five years before. The pain was constricting in character and localized over the precordium and down the left arm. These attacks during the past five years were brought on by extreme exertion and were fleeting in character. As time went on, the severity of the pain became markedly aggravated and the frequency increased to as many as two to three attacks daily. He used nitroglycerin constantly. In fact, he dared not move about without having the drug with him. Eight months before the injection, his condition became extremely aggravated. His repeated attacks during the day were severe and agonizing, persisting for ten or fifteen minutes and requiring nitroglycerin and absolute cessation of activities. During the night, he was frequently awakened by these severe attacks. There was with each attack the fear of impending death.

Physical examination showed an extremely enlarged heart and aorta. No adventitious sounds were heard. The heart sounds were faint and distant. His blood pressure was systolic 145 mm. and diastolic 80 mm.

On October 27, 1925, a paravertebral injection of alcohol was done on the left side. Seven cubic centimeters of an 85 per cent solution of alcohol were introduced into the first, second, third, fourth, fifth, sixth, seventh, eighth and ninth dorsal nerves.

The following are the sensory findings observed before and after the injections:

October 26, 1925, before the injection.

A. Epicritic sensibilities. (1) A zone of hyperesthesia to light touch with cotton wool extended over the skin segments supplied by the first to the ninth dorsal nerves, posteriorly and anteriorly. (2) Discriminating powers for temperatures ranging between 20 and 38° C. were intact. (3) Tactile localization was normal.

B. Protopathic sensibilities. (1) A zone of hyperalgesia to pin prick extended on the left side of the skin segments supplied by the first to the ninth dorsal nerves. (2) A marked hyperthermalgesia was noted over the above corresponding skin segments. There was observed no abnormality in his ability to differentiate extremes of temperature.

March 1, 1926. One hundred and twenty-five days after injection.

A. Epicritic sensibilities. (1) A zone of hypesthesia was observed to extend over the skin areas that previous to injection showed hyperesthesia. In fact, he hardly perceived the stroke of the cotton wool. (2) A marked hypothermesthesia was observed. He found great difficulty in differentiating fine degrees of temperature. (3) Cutaneous localization became greatly impaired.

B. Protopathic sensibilities. (1) Instead of the previous hyperalgesia extending over the first to the ninth dermatomes, a marked hypalgesia almost approaching analgesia was observed. (2) His ability to feel extremes of temperature was greatly impaired.

Case Summary. (1) Before injection a zone of dermatomic irritability extended from the first to the ninth dorsal nerves on the left side. Sensory examination, one hundred and twenty-five days after the injection showed that the nerve conductivity was greatly reduced. (2) His condition at present is as follows: (*a*) He requires no nitroglycerin. (*b*) The attacks of pain although still present are exceedingly mild and fleeting. Before injection they lasted ten to fifteen minutes, or as long as an hour, requiring large doses of nitroglycerin. The pains were so excruciating as to cause extreme anguish and fear of impending death. The pains now are very light and transitory, disappearing in a few seconds. There has been only one attack of pain during the night since the injection. His attacks of pain before injection alarmed his family exceedingly because of the general picture of extreme misery that he presented. Now the family is hardly aware that he has an attack of pain. He has now been comfortable for eighteen weeks.

Summary. This paper is presented to correlate our previously observed clinical findings in patients complaining of severe cardiac pain with the information obtained by others through animal experimentation. The clinical observations showed, that subjectively, the pain was relegated to areas of the skin which were supplied by nerves arising between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7). These very same skin areas to which the patients subjectively referred the pain showed them to be hypersensitive to protopathic tests (Head Zones). These findings indicated that the pain impulses were passing through the rami communicantes and ganglia, which were to be found between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7). The indifferent operative results ensuing from procedures upon the cervical sympathetic chain and other nerves in the neck indicated by their failure to ameliorate the pain, that the painful charges were not passing through these structures in their course to the sensorium. A review was made of 41 patients suffering from severe cardiac pain, who were treated by paravertebral block. The injections were confined to those rami communicantes found between the eighth cervical and seventh (C 8 to D 7) spinal segments. The gratifying results obtained seem to quite directly suggest that these rami

communicantes and ganglia are the true conveying pathways of the pain impulses to the spinal cord so as to reach the spinothalamic tracts. The résumé of the animal experimentation supports the clinical observations. This showed clearly that the impulses were passing up through those rami communicantes and ganglia found between the eighth cervical and sixth thoracic. Such nerves as the depressor nerve and the vertebral nerve, rarely observed in humans, were stimulated in animals and failed to incite painful reactions. A perusal of all the data indicates quite clearly, that the future surgical procedures for the relief of cardiac pain must have their attention relegated to the rami communicantes found between the eighth cervical and seventh thoracic spinal segments (C 8 to D 7).

BIBLIOGRAPHY.

1. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Am. Heart J., 1926, **1**, 393.
2. Ionescu, D.: Experimental Contribution to the Knowledge of the Sensory Cardio-aortic Tracts, Ztschr. f. klin. Med., 1928, **7**, 415.
3. Jonnesco, T.: Presse méd., 1921, **29**, 193.
4. Danielopolu and Hristide: Bull. et mém. Soc. méd. d. hôp. de Paris, 1923, **47**, 69.
5. Lilienthal, H.: Arch. Surg., 1925, **10**, 531.
6. White, J. C., and White, P. D.: Angina Pectoris Treatment with Paravertebral Alcohol Injection, J. Am. Med. Assn., 1928, **90**, 1099.
7. Mandl, F.: Wien. klin. Wchnschr., 1925, **38**, 759–760.

CLINICAL AND ROENTGEN RAY FINDINGS IN THE STUDY OF THE HEART AND THE GREAT VESSELS.*

STUDY OF 100 CASES FROM THE CARDIAC CLINICS OF THE PHILADELPHIA GENERAL HOSPITAL.

BY GERTRUDE JACKSON CHANDLEE, M.D.,

VISITING CHIEF OF CARDIAC CLINIC, DIVISION OF CARDIOLOGY, PHILADELPHIA GENERAL HOSPITAL,

AND

E. BURVILL-HOLMES, M.D.,

CHIEF OF ROENTGEN RAY LABORATORY, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA.

(From the Department of Cardiology and the Roentgen Ray Department of the Philadelphia General Hospital.)

DURING the past thirty years of Roentgen ray investigations, various students of the cardiovascular system have emphasized certain aspects of the Roentgen ray examination of the heart and great vessels. Zinn,[1] in 1898, made a diagnosis of patent ductus

* Read at the Philadelphia Roentgen Ray Society, October 6, 1927.

arteriosus on the basis of a systolic murmur heard in an area of dullness in the third interspace to the left of the sternum and a marked systolic pulsation seen in the region of the pulmonary artery on fluoroscopic examination. Groedel,[2] in his treatise on the Roentgen ray examination of the heart and the aorta, includes fluoroscopic examinations, but, more particularly, Roentgen ray plates of the characteristic silhouettes of the various cardiovascular lesions. Groedel's studies are made in correlation with electrocardiographic studies and in respiratory phases, and with orthodiagraphic tracings, and include precise measurements of the heart and great vessels. Assmann's[3] work on the heart adds a great deal to studies of the pulmonary area, and, perhaps, more exact data on congenital heart disease from a Roentgen ray standpoint than previous writers. He also ascribes a shadow to the left of the heart as due to syphilitic aortitis. The work of Vaquez and Bordet[4] can best be summed up as an exhaustive study of the heart and the aorta, with orthodiagraphic studies made in well-defined positions, with teleradioscopic, teleradiographic and clinical findings. McPhedran and Weyl[5] have made Roentgen ray studies of the chest during different phases of the cardiac cycle, particularly in diastole of the heart, and also during different phases of respiration with the purpose of defining more clearly lung pathology. The first work by Roentgen ray in the differential etiology of cardiac disease of infectious origin was probably done by Ledbetter, White and Holmes[6] in reference to the causes of aortic regurgitation, the supracardiac shadow due to syphilis being absent in aortic regurgitation due to other causes, notably rheumatic fever. The importance of this finding is evident from the vast difference in the prognosis and therapy in these two forms of cardiac disease.

Abreu,[7] in the radiologic study of the great vessels, uses anatomic preparations in corroborating his Roentgen ray technique in vascular shadows and their differentiation, as well as exact studies of the aorta in well-defined positions. Pendergrass[8] emphasizes Roentgen ray studies in lateral views of the heart with more exact observations on the cardiodiaphragmatic area, the normal straight shadow seen in this area being interpreted as a composite shadow of the reflection of the pericardium to the left diaphragm, the inferior vena cava and the posterior phrenopericardial ligaments. This shadow is best seen in the left lateral position with the left side next to the film. Distortion of this shadow is found in adhesive pericarditis and in pericarditis with effusion. In pericarditis with effusion, this work is invaluable when surgical procedures are indicated, more particularly when pericardiocentesis is done posteriorly. Pendergrass further demonstrates the value of lateral Roentgen ray study in determining the site and size of aneurysms of the aorta, in which the distance of the aneurysm from the chest wall must be determined before wiring can be employed as a surgical measure for the relief of cardiovascular disease.

In the present study, we have attempted to study the heart, particularly in phases of respiration, with the purpose of determining the effect of this process on the circulation as seen with Roentgen ray and of throwing more light on the physiology of the cardiovascular and respiratory mechanism. Our object has been also to correlate more definitely Roentgen ray studies with clinical findings in the diagnosis of cardiovascular disease.

All patients are primarily subjected to a fluoroscopic examination. The degree of pulsation, the presence or absence of arrhythmias, changes in the normal cardiac silhouette, dilatation of the aorta, enlargement or marked pulsation of the pulmonary area, presence of aneurysm, ventricular hypertrophy and presence or absence of pericardial adhesions are noted. This examination includes fluoroscopic studies in the anterior-posterior positions, the right anterior oblique position for more exact study of the pulmonary area, lateral positions for study of the mediastinal space and pericardial adhesions, and the right posterior position. The lateral bending positions in the anterior-posterior position also demonstrate the low and fixed position of the apex sometimes seen in adhesive pericarditis. These examinations are made during phases of inspiration and expiration. Left ventricular hypertrophy is estimated in the right posterior position with the patient in varying angles. We have found in a series of normal hearts that the apex of the heart should disappear behind the left border of the spine at approximately 40 degrees or less. If an angle of 45 degrees is necessary to cause such disappearance, we regard hypertrophy as probable and as certainly present in excess of that. Error results unless care is taken that the central ray passes through the cardiac shadow at right angles to the spine.

In addition to fluoroscopic studies, films are made at two meters distance, the target being centered over the spine on a level with the angles of the scapulæ. The patient should be instructed to hold his breath at the end of quiet inspiration. We have made a series of comparative films on normal and obese patients, and on patients with endocardial and congenital heart disease, at the end of deep inspiration, sustained with the glottis closed, and at the end of deep expiration sustained with the glottis closed, and during quiet sustained inspiration. The changes in the cardiac silhouette were somewhat more apparent in those made during deep inspiration, sustained with the glottis closed, but the comparative changes in the silhouette of the cardiac areas were easily visualized in all phases of respiration and in the different types of patients.

From the films, we confirm and correlate our fluoroscopic findings. The transverse diameter of the heart, aorta and the chest are measured. The measurement of the chest is taken from the inner border of the ninth rib, just below the diaphragm in place of the dome of the latter which some prefer as a basal chest measurement.

We arbitrarily consider the heart to be enlarged if the transverse diameter is over 50 per cent of that of the chest.

We find that the normal heart shows, diagramatically, one curve on the right side, that of the right auricle and right auricular appendage. The left border has four curves: the arc of the aorta, the arc of the pulmonary artery, of the left auricle and that of the left ventricle. In the cardiac silhouette by fluoroscope and film, the curves of the pulmonary artery and the left auricle are not definitely differentiated (Fig. 1*a*). Indeed, we are of the opinion that when this differentiation is demonstrable, the heart is definitely abnormal. Groedel[2] observes that the character of pulsation of the pulmonary artery and the left auricle, differentiates these two areas. Abreu[7] gives as visible contours, "the right auricle, the superior vena cava, partly covered by the right bronchus; the arch of the aorta which hardly extends beyond the spinal column; the commencement of the descending aorta, the remaining part being invisible because of the pulmonary artery; and the left ventricle."

From the functional behavior of the heart and great vessels during phases of respiration, in the course of fluoroscopic examination, and from the study of the cardiac silhouette on films, we have classified hearts as inspiratory in type or expiratory in type. In quiet respiration, there is little change in the cardiac contour in normal or in diseased hearts, or in those with congenital defects as comparative plates show. In deep inspiration sustained with the glottis closed, there are marked changes in the silhouette of normal hearts[9] and less change in the silhouette of diseased hearts (Fig. 8*c*, *d*, *e*, *f*). In forced inspiration, the cardiac shadow is better defined, partly due to greater contrast in shadows as a result of increased aëration of the lungs and partly due to the respiratory effect on the circulation and behavior of the heart during respiration. The electrocardiographic tracing taken during phases of respiration: quiet respiration, forced inspiration and forced expiration in each of the usual three leads, show marked respiratory variations in the rate of the heart beat and in the amplitude of the waves in the three leads (Fig. 2) which correspond to changes in the heart silhouette and behavior of the heart during these phases of respiration. Pulsations are apparently more forceful in inspiration as demonstrated by fluoroscopic examination. Murmurs are best heard on deep sustained expiration as the heart is apparently nearer the chest wall, possibly because of some intrinsic circulatory phenomenon.[10] Clinically, we find the disappearance of murmurs on deep sustained inspiration, and the reappearance of murmurs on deep sustained expiration. This is of diagnostic importance in detecting murmurs, particularly in congenital heart disease.

We have found in the obese patient an expiratory type of heart, with usually increased measurements on deep sustained inspiration, and conversely decreased measurements or no change in measure-

ments on deep sustained expiration, in contradistinction to the measurements usually found (Fig. 1*b*, *c*, *d*, *e*). We believe that the heart normally rotates posteriorly on deep inspiration, due to the descent of the diaphragm and the attached pericardial ligaments. In the obese patient with a high diaphragm, we believe that the heart rotates anteriorly on deep inspiration or shows no change of position, remaining transverse. In the normal heart, the ventricular measurements are decreased on deep inspiration and increased on deep expiration. The electrocardiogram of the obese patient usually shows left axis deviation (Fig. 3). There may be hypertrophy of the heart and it may be questioned if this type of heart is normal or at least normal in physiology. The obese patients show dyspnea on exertion and it may be that the anatomic change in the position of the heart and resultant effect on the great vessels due to rotation and torsion is a mechanical factor in causing the dyspnea as well as an explanation for the anatomic change of electrical axis.

The silhouette of the "Schlaffen heart" (Groedel[2]), we think, corresponds to the expiratory type of heart and to the obese type with a high diaphragm (Fig. 1*d*, *e*). In tracheal obstruction, with increased negative pressure, we believe the heart is inspiratory in type (Pendergrass,[8] Fig. 209). The vertical type of heart seen in tuberculosis (Fig. 5*a*) and emphysema, we consider inspiratory in type. We observe the inspiratory type of heart in mitral stenosis (Fig. 5*b*). We have found, in this series of 100 cases of heart disease, that hearts that are not normal, approach one or the other of the two types of hearts from a Roentgen ray and clinical standpoint. The silhouette of the inspiratory type of heart corresponds to the normal heart during forced inspiration and is vertical in position. The expiratory type of heart corresponds to the normal heart during forced expiration and is transverse in position. These two types of hearts we believe correspond to variations in vital capacity. Campbell[11] observes a decreased vital capacity in mitral stenosis and shallow breathing, which seems to agree with our observations on the inspiratory type of heart. We believe that these two types of hearts correspond also to variations in intrathoracic pressure and to variations in intrathoracic and intraäbdominal pressure relations during respiration, and to variations in the capillary circulation in the lungs. Wagoner,[12] in experimental work in animals, found that amounts of fluid aspirated intraäbdominally varied with the size of the animal and its type of breathing. Intraäbdominal negative pressure increased during inspiration and greater amounts of fluid were aspirated, the deeper and more rapid the breathing. Groedel[13] speaks of the shift of the blood during inspiration and expiration as a protective mechanism, particularly in diseased conditions of the cardiovascular system. Abnormally high or low insertions of the diaphragm, mechanical interference in the heart itself due to valvular lesions, with hypertrophy of the heart and pressure changes in

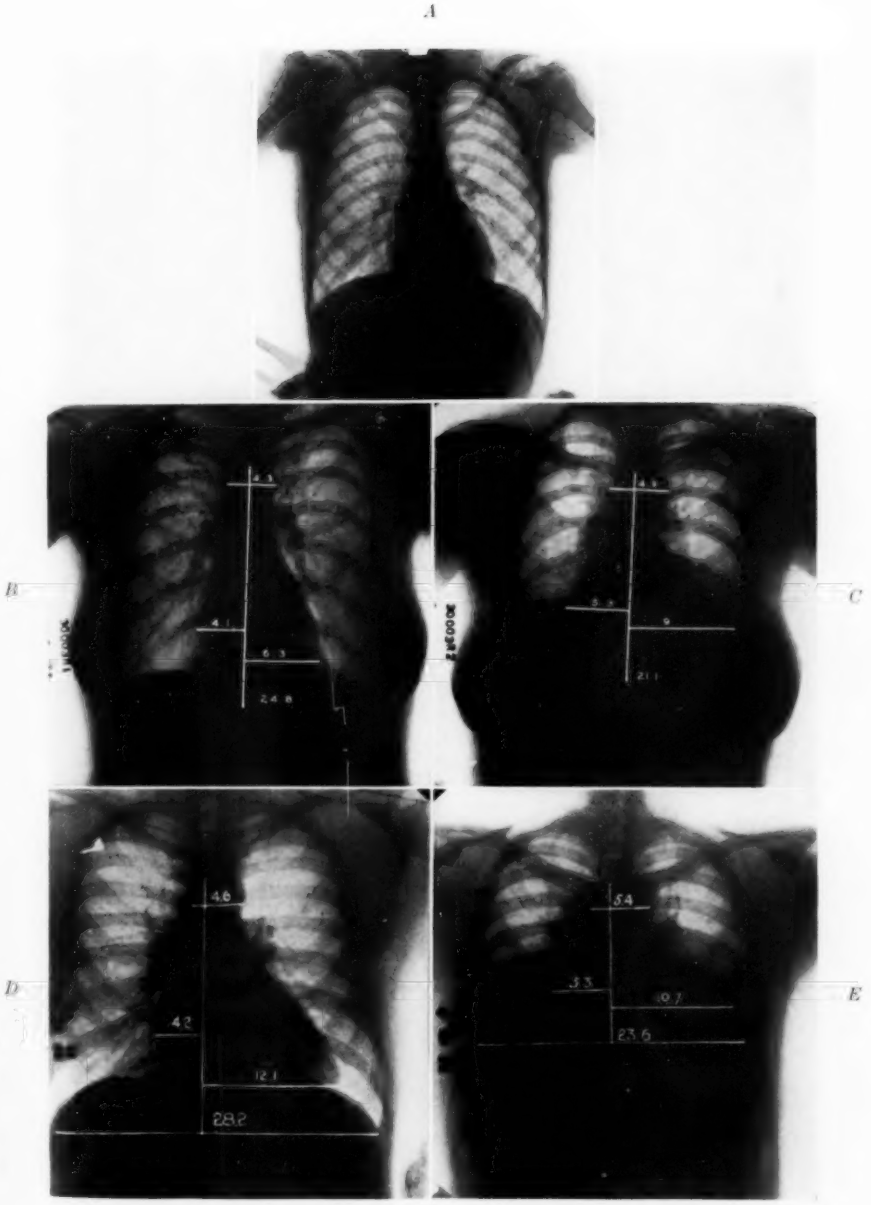


FIG. 1.—*A*, child, quiet respiration; *B*, adult, forced inspiration; *C*, same in forced expiration. Obese type. *D*, adult, forced inspiration; *E*, same in forced expiration. Note paradoxical change in measurements due to forward rotation during inspiration.

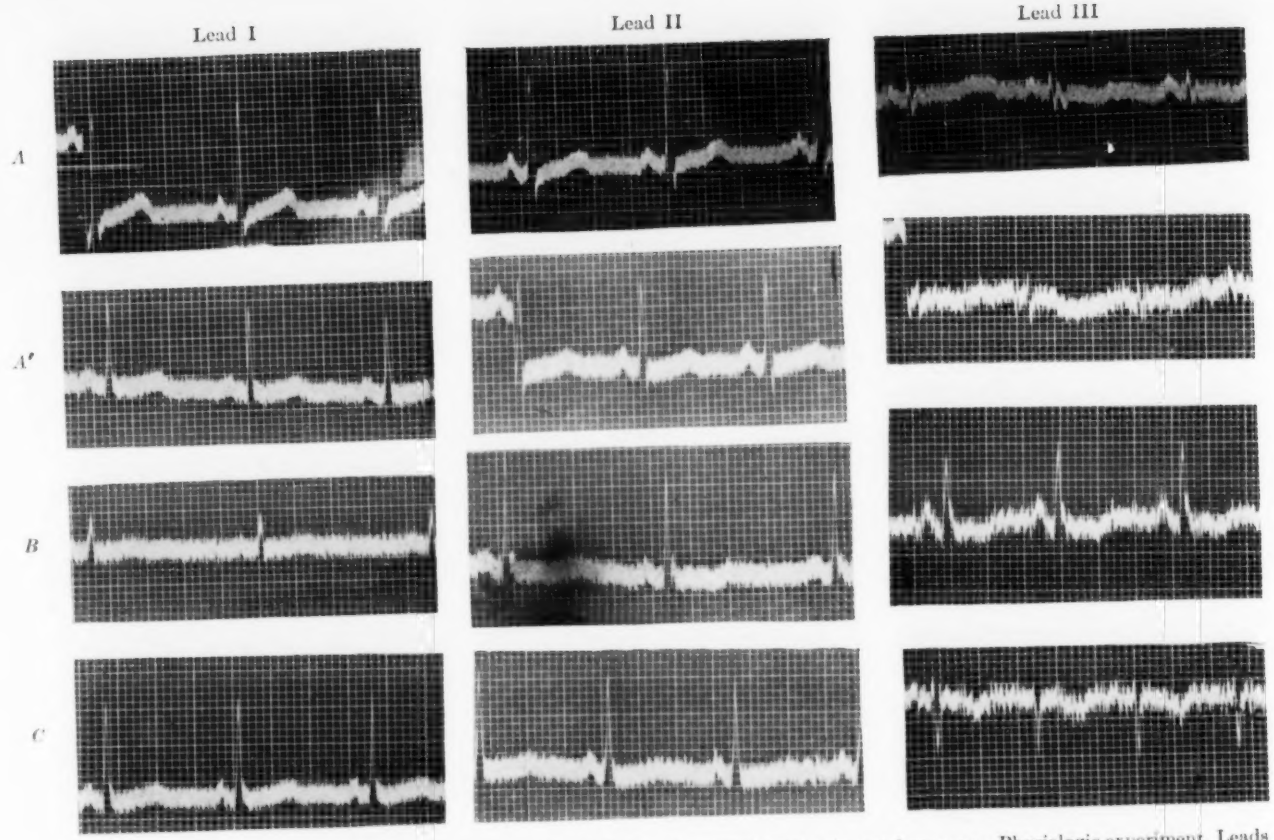


FIG. 2.—Electrocardiographic tracing on normal (Fig. 1 *B*, *C*). *A*, normal tracing in usual manner. Physiologic experiment, Leads I, II, III. *A'*, quiet respiration; *B*, forced deep inspiration sustained with glottis closed; *C*, deep expiration, sustained with glottis closed. (Note change in rate and amplitude of waves.)

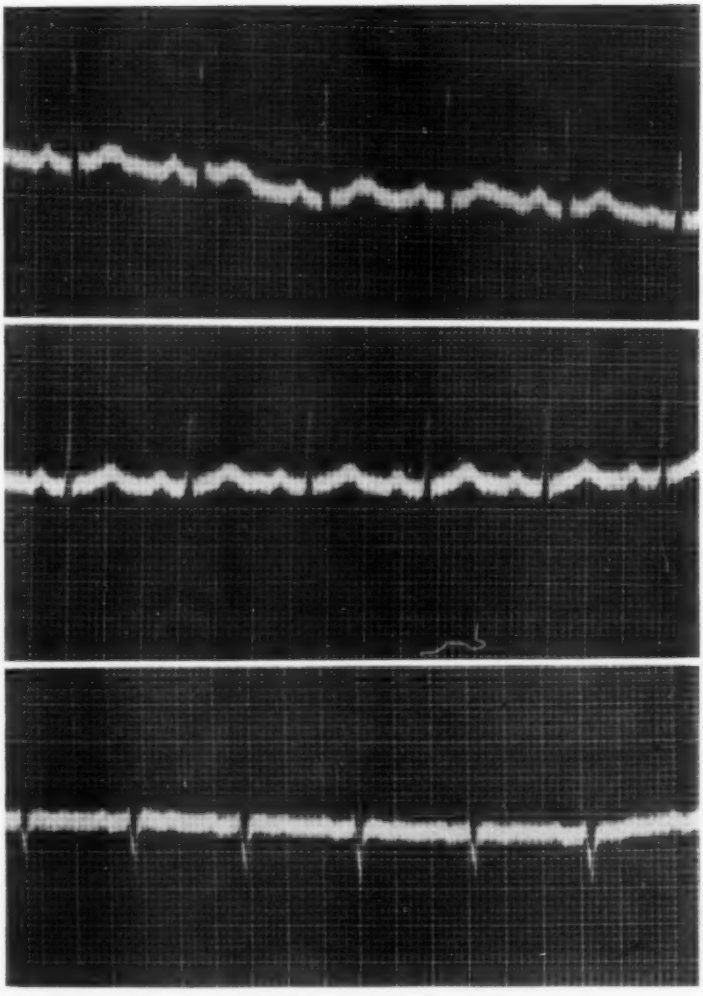


FIG. 3.—Electrocardiogram on obese patient (Fig. 1 *D*, *E*) taken during quiet respiration. Note left axis deviation of *Q–R–S* group.

FIG. 2.—Electrocardiographic tracing on normal (Fig. 1 *B*, *C*) ... I, II, III. *A*, quiet respiration; *B*, forced deep inspiration sustained with glottis closed; *C*, deep expiration, ... closed. (Note change in rate and amplitude of waves.)

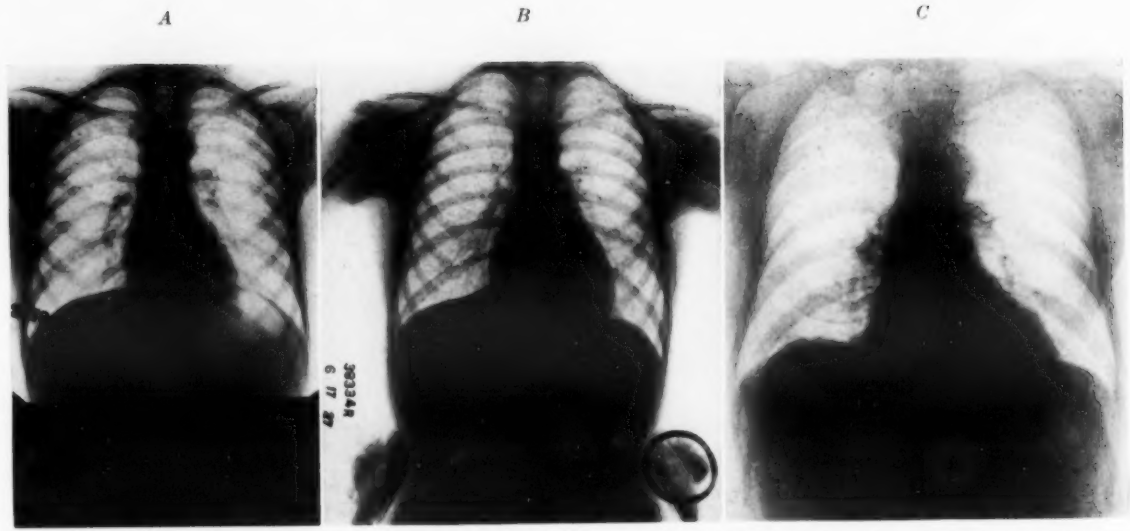


FIG. 4.—Overactive heart. *A*, normal silhouette with bulge of aorta; *B*, note bulge over the pulmonary area; *C*, note bulge of aorta due to hypertension in adult.

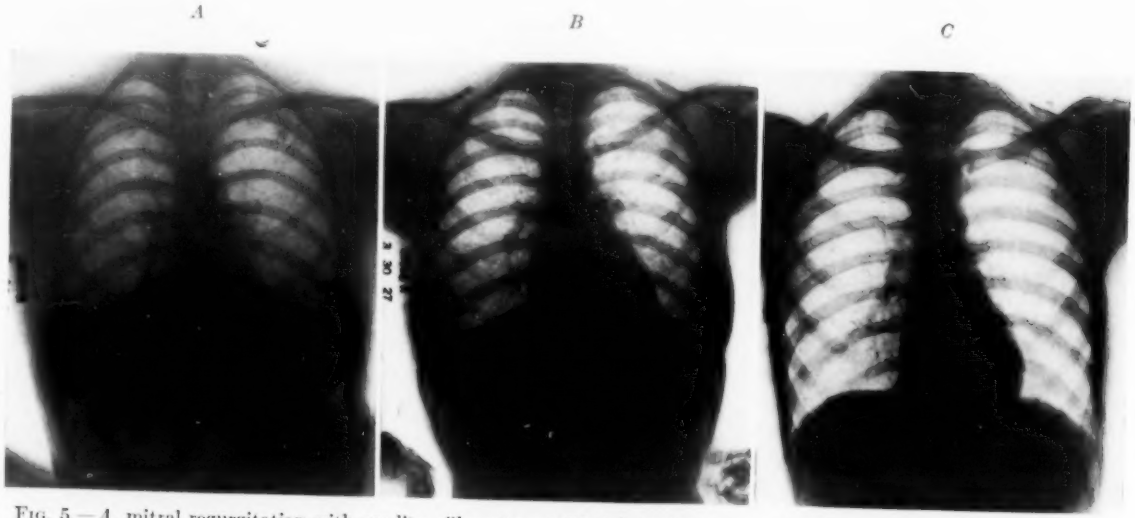


FIG. 5.—*A*, mitral regurgitation with cardiac silhouette modified by tuberculosis; *B*, early mitral stenosis—note straight left border due to hypertrophied left auricle (inspiratory type of heart); *C*, early mitral disease, no change in cardiac silhouette.

A B

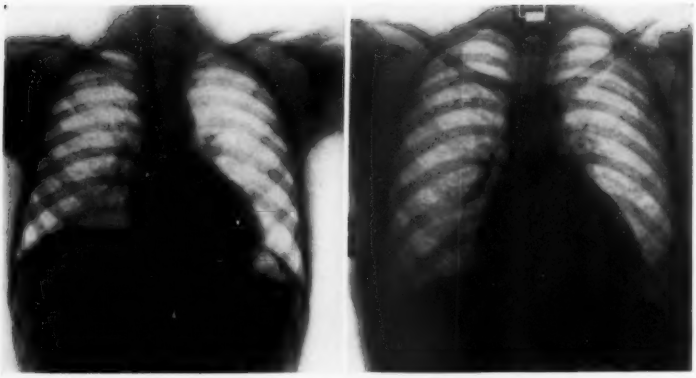
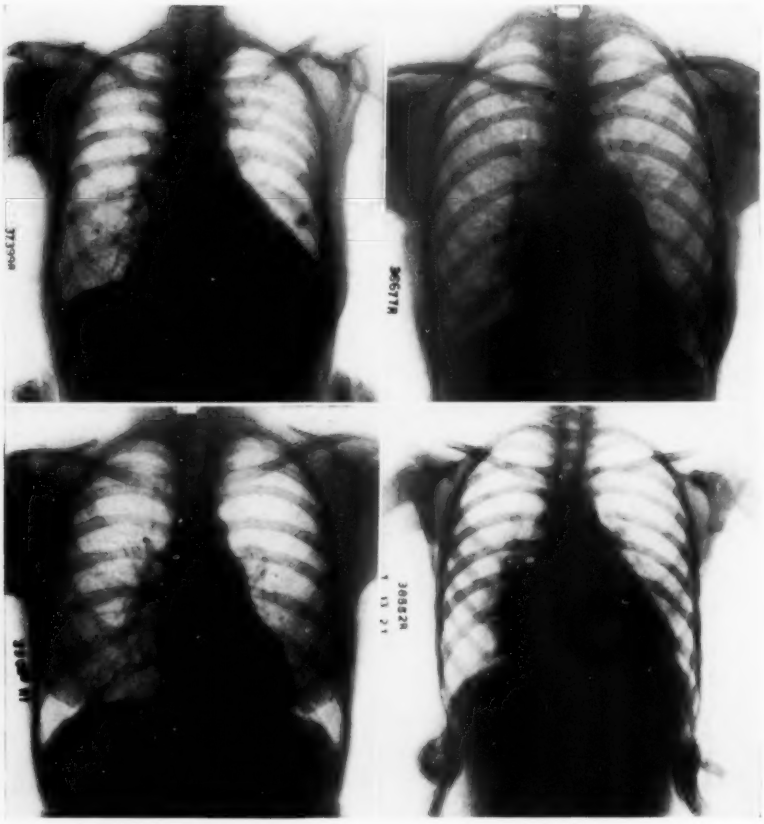


FIG. 6.—Mitral regurgitation. *A*, child; *B*, adult.

A B



C D

FIG. 7.—Mitral regurgitation. *A*, with mitral stenosis; *B*, primary mitral stenosis; *C*, with acquired pulmonary stenosis—note bulge over pulmonary arc; *D*, with all valves involved except those of pulmonary artery. (Note hypertrophied right side of the heart due to tricuspid regurgitation).

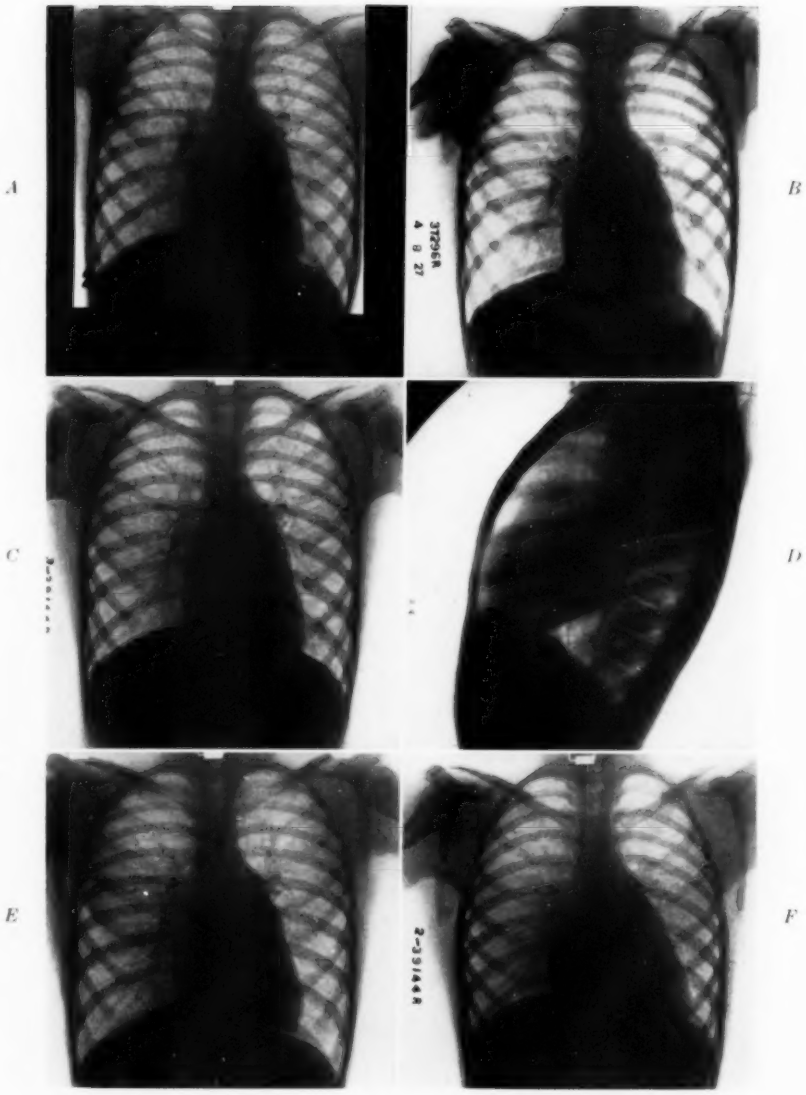


FIG. 8.—Comparative study of mitral stenosis with pulmonary dilatation; patient growing progressively worse. Dilatation of pulmonary artery with diastolic murmur at times, early signs of decompensation with passive congestion. *A*, May, 1925; *B*, April, 1927; *C*, forced inspiration; *D*, lateral, quiet respiration; *E*, quiet respiration; *F*, forced expiration; *C*, *D*, *E*, *F*, August, 1927. Inspiratory type of heart.

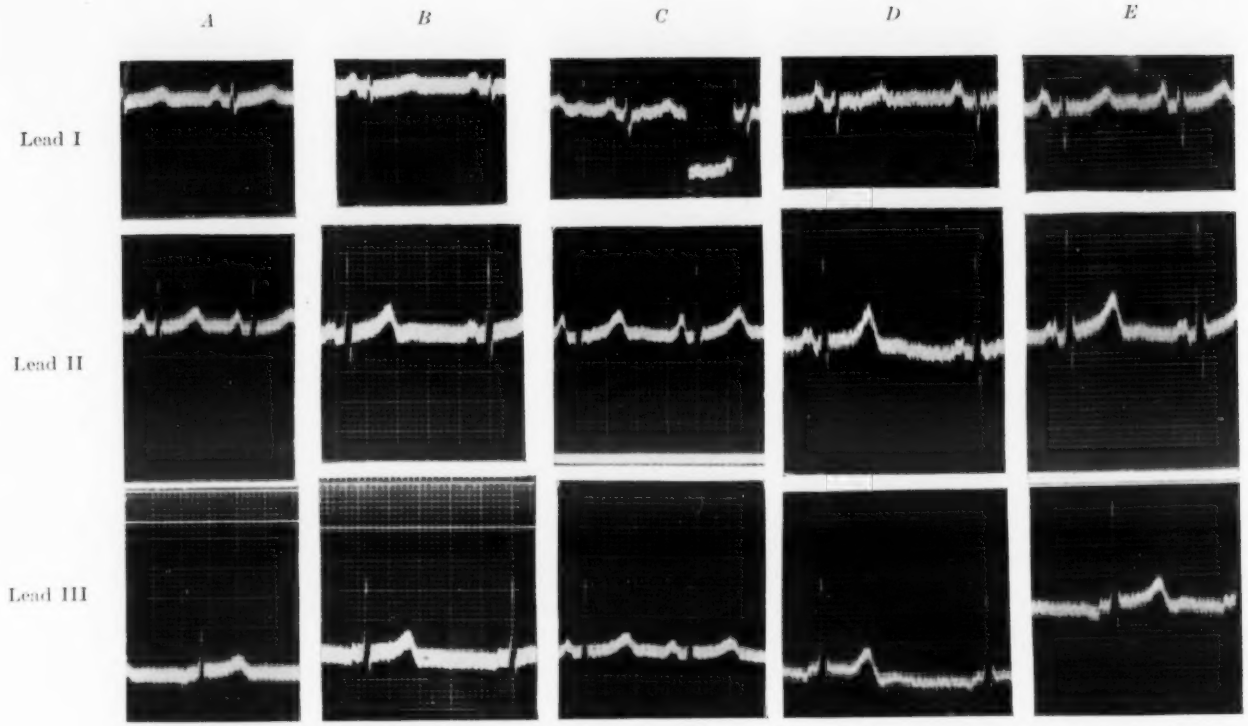


FIG. 9.—Progressive electrocardiographic changes, showing increasing right axis deviation and increasing amplitude of *T* wave. Patient of Fig. 8. *A*, November, 1923; *B*, December, 1923; *C*, May, 1925; *D*, April, 1927; *E*, September, 1927.

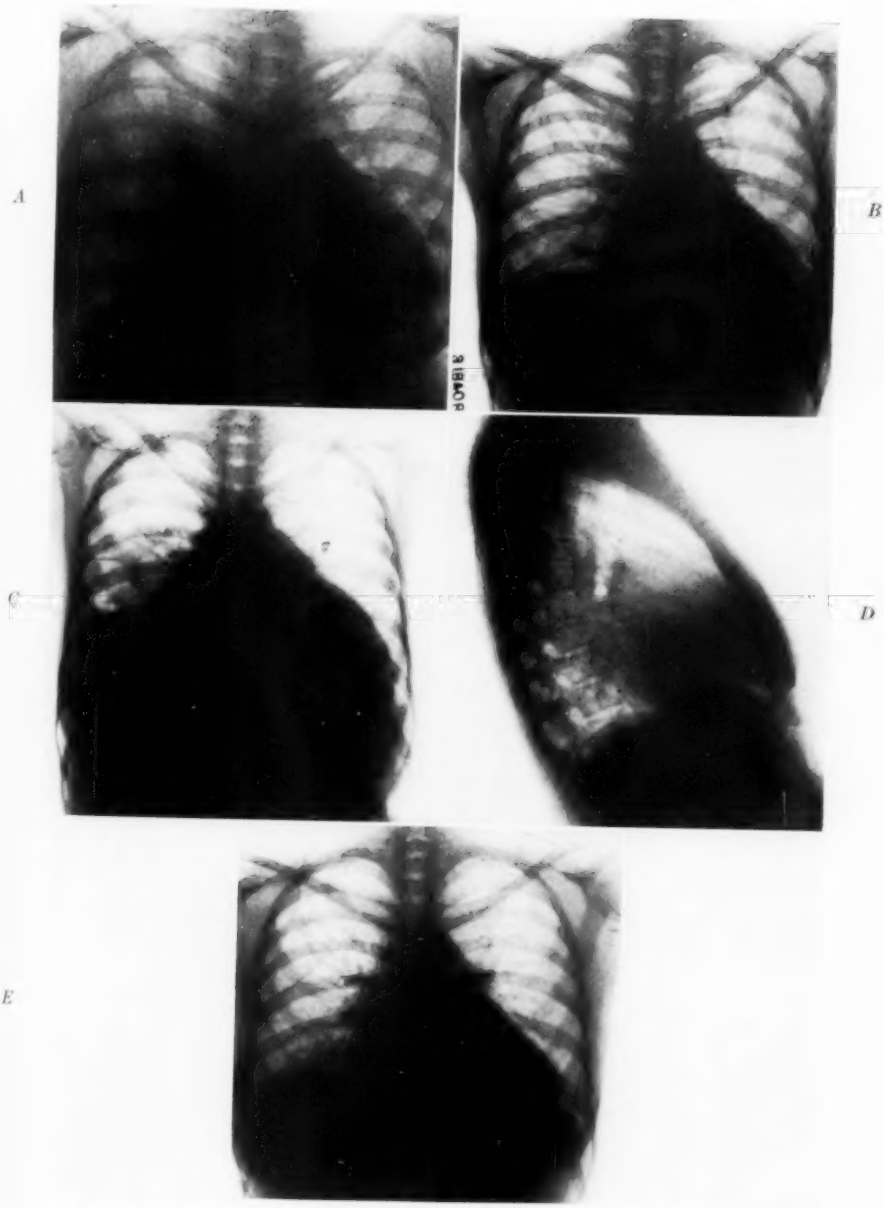


FIG. 10.—Terminal results of endocarditis (mitral regurgitation and stenosis associated with pulmonary and aortic regurgitation, probably also tricuspid regurgitation). *A*, January 25, 1926; *B*, March 19, 1926; *C*, December 3, 1926; *D*, *E*, June 2, 1927.

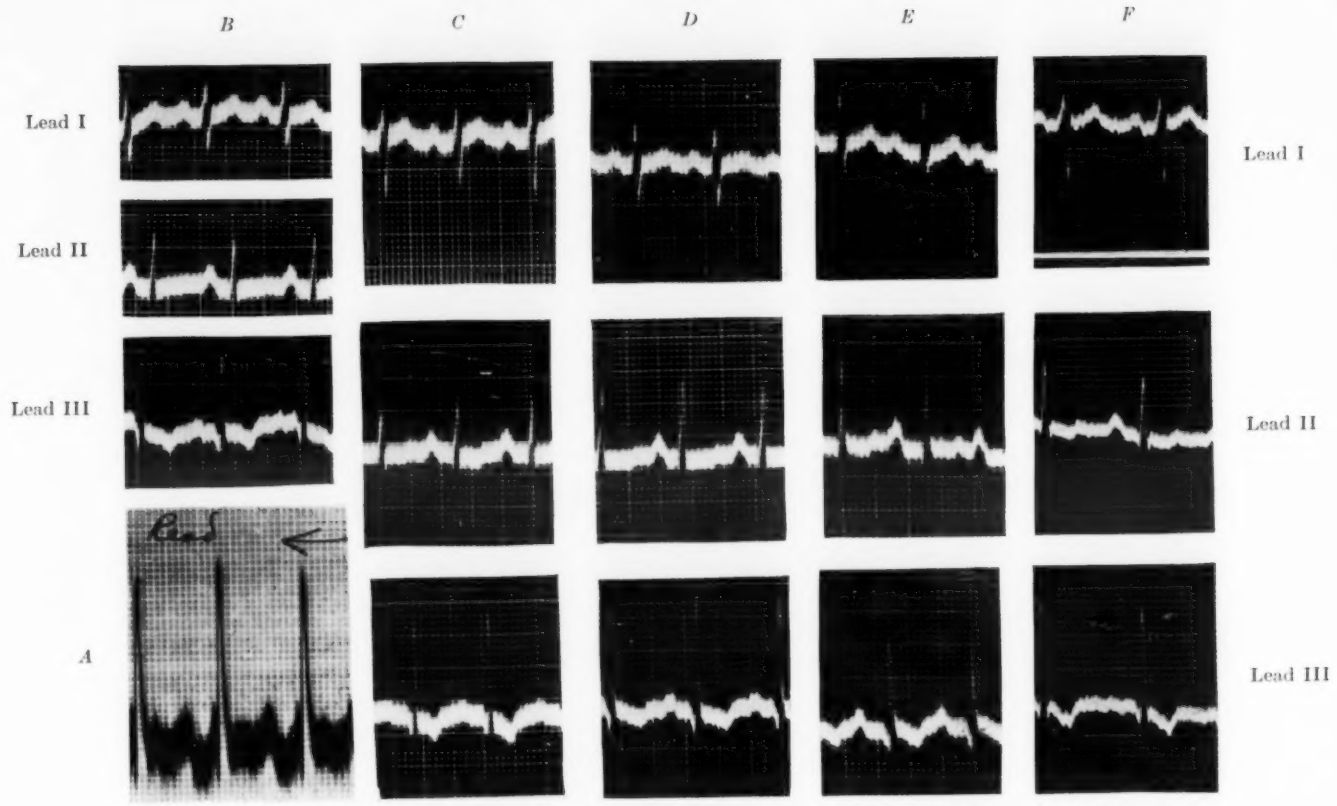


FIG. 11.—*A*, radial pulse tracing, January 15, 1926, collapsing type, seen in aortic regurgitation. (Aortic diastolic murmur in presence of pulmonary diastolic murmur.) Electrocardiographic tracings showing changes in axis deviation and slight changes in *P* and *T* waves. *B*, January 15, 1926; *C*, February 5, 1926; *D*, March 8, 1926; *E*, March 19, 1926, *P-R* interval slightly prolonged; *F*, December 3, 1926.

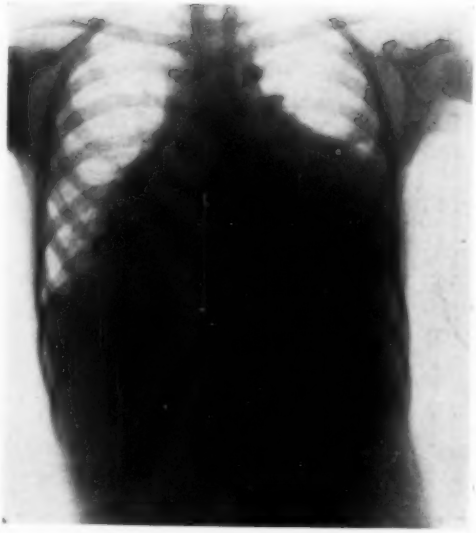


FIG. 12.—Pericarditis with effusion.

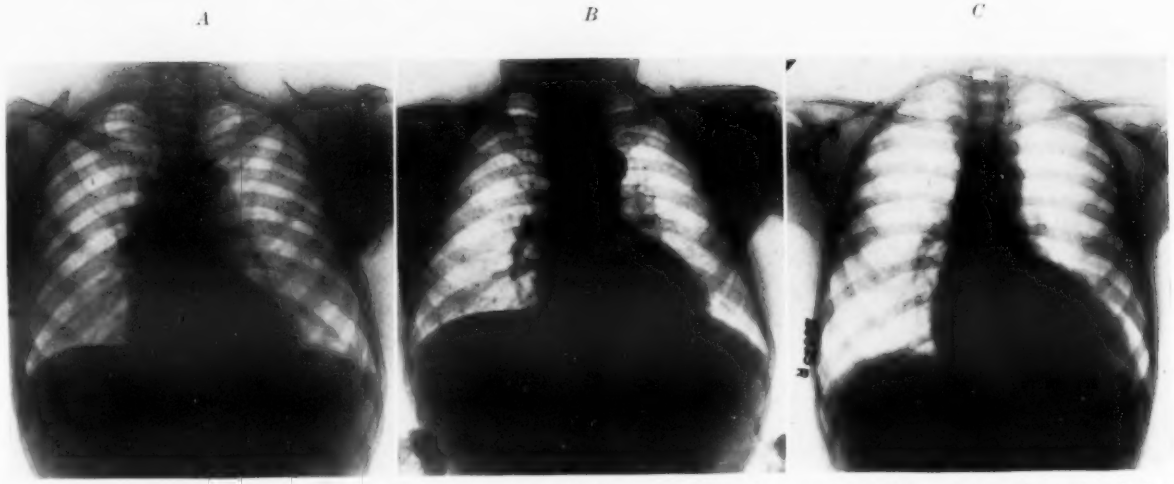


FIG. 13.—Aortic regurgitation. *A*, syphilis—note the dense shadow to the left of upper mediastinum below the arch (shadow of associated aortitis); *B*, syphilis, no associated shadow of aortitis as in *A*; *C*, rheumatic heart disease.

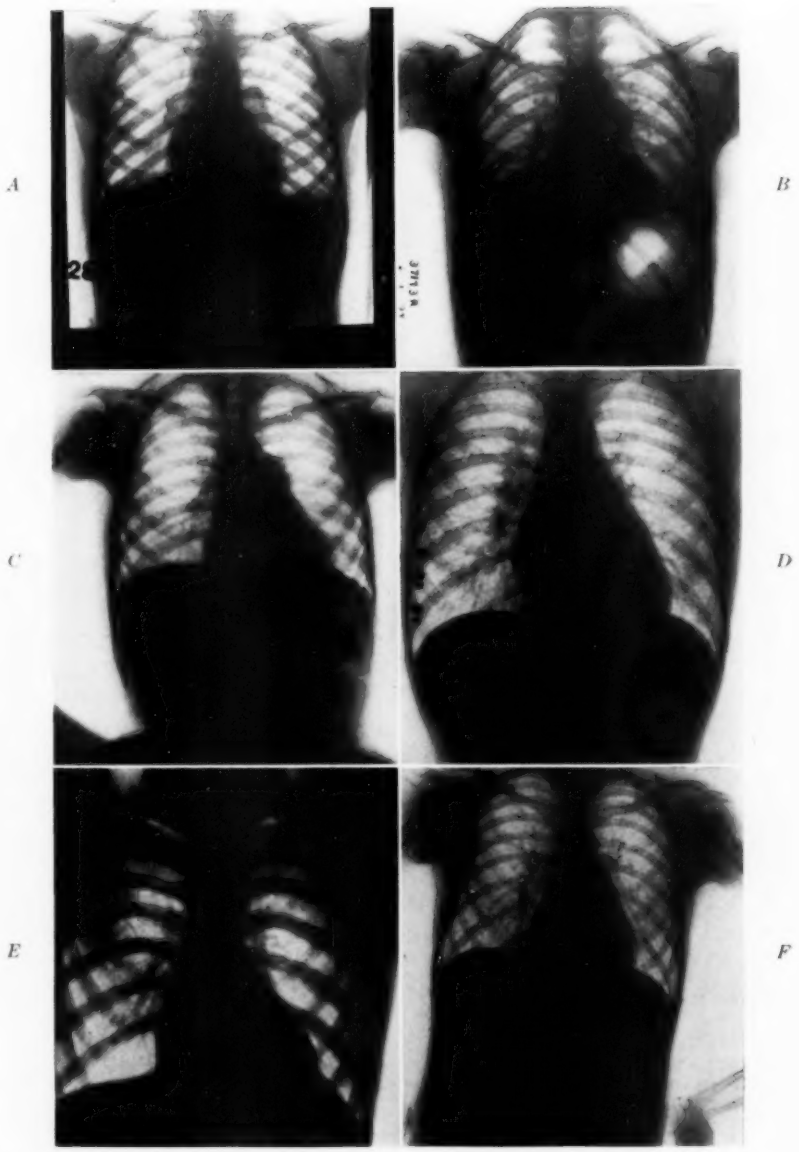


FIG. 14.—Congenital heart disease. *A*, clinically, patent ductus arteriosus, confirmed by fluoroscopic examination; normal silhouette; *B*, patent ductus (note bulging over the pulmonary arc); *C*, patent ductus with septal defect (two distinct murmurs heard); *D*, congenital pulmonary stenosis; no bulging over the pulmonary arc; *E*, congenital pulmonary stenosis; autopsy examination showed presence also of septal defect; note more globular type of heart than *D*; *F*, mitral regurgitation with question of congenital heart (patent ductus) or acquired pulmonary stenosis. Silhouette would militate against diagnosis of patent ductus.

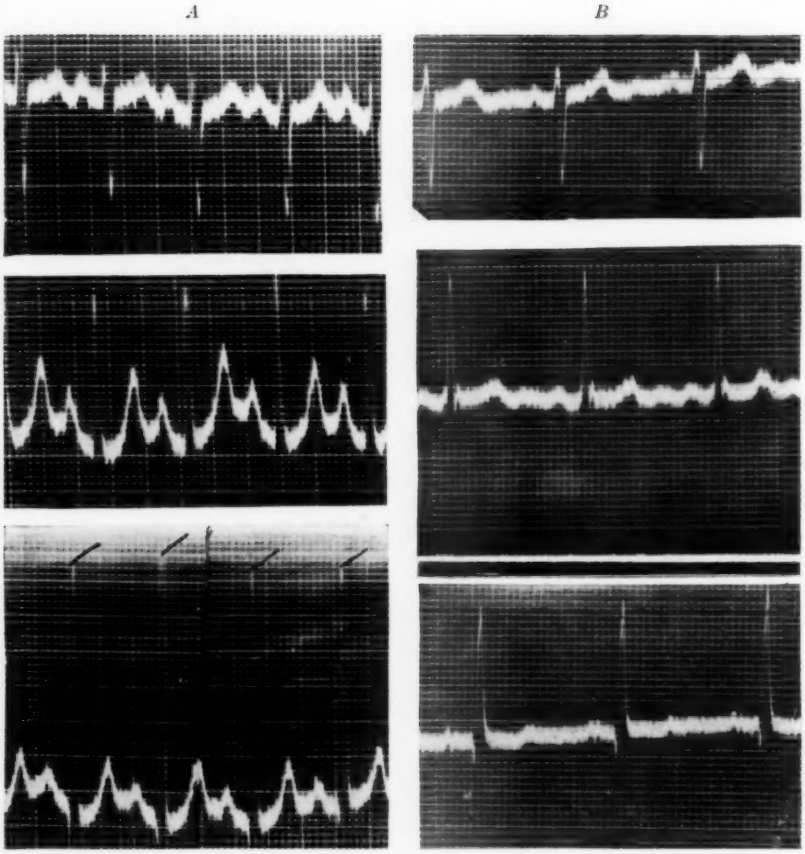


FIG. 15.—Electrocardiograms in pulmonary stenosis, congenital. *A*, marked right axis deviation and marked increase in amplitude in *T* wave. Corresponds to patient 14-*D* (pulmonary stenosis); *B*, marked right axis deviation; corresponds to patient 14-*E* (pulmonary stenosis with septal defect).

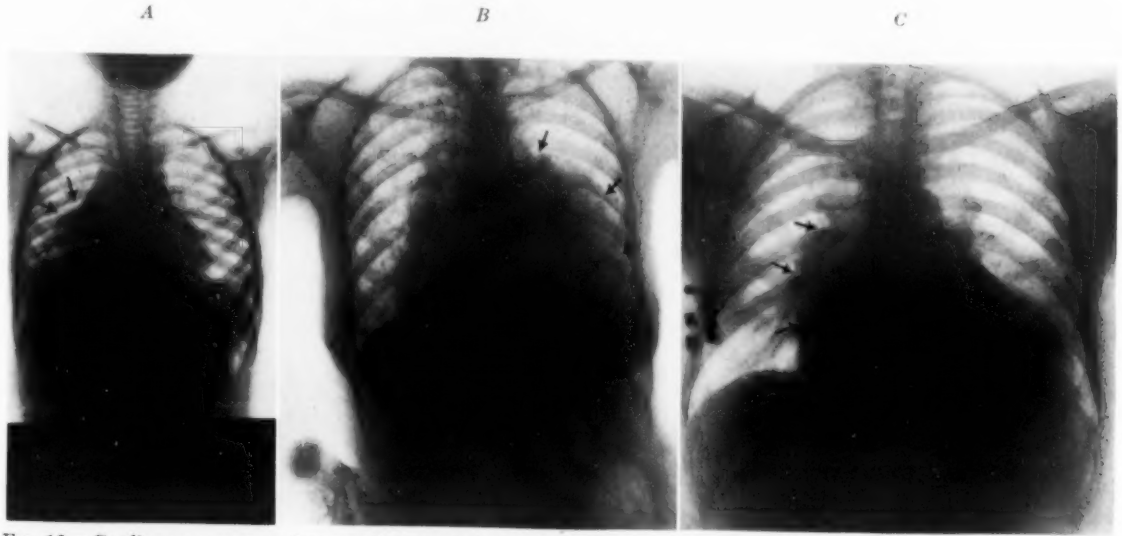


FIG. 16.—Cardiac aneurysms. *A*, congenital septal defect between aorta and base of right ventricle, aneurysm also of right ventricle; *B*, aneurysm of left ventricle, congenital in origin; *C*, acquired aneurysm of right auricle.

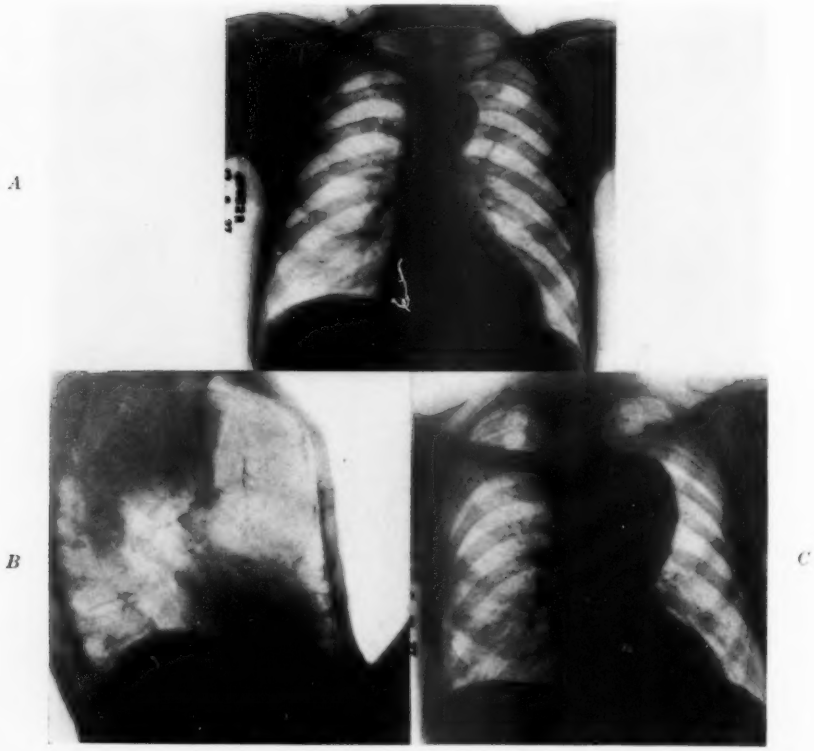


FIG. 17.—*A*, arterial sclerosis, chronic lead poisoning; no endocardial disease; note upward tilting of the shadow of aortic arch; *B*, enormous saccular aneurysm of horizontal arch of aorta; note atheromatous plaques throughout the course of aorta from its origin to the termination of its thoracic division; *C*, lateral view of *B*.

the great vessels, changes in the hydrogen-ion activity of the blood and carbon dioxid content controlling respiration, decrease in the capillary field due to disease of the lungs and decreased bloodflow, tracheal obstruction, atonicity of the heart muscle or faulty habits of breathing may also be factors involved. We believe, however, that from a Roentgen ray and clinical standpoint this functional classification of hearts as inspiratory or expiratory in type is explanatory and is not an arbitrary deduction from the study of the cardiac silhouette by fluoroscope and film, but that it is based on definite normal and pathologic physiology underlying the mechanism of respiration and fluid distribution in the body and that further study along these lines may demonstrate principles of value in surgical procedures in the chest, particularly in the "rationale" of removal of fluid by surgical intervention. Such study may demonstrate indications general measures along the therapeutic lines of the physical factors involved, particularly in relation to intraäbdominal and intrathoracic pressures and the muscular tension of the abdominal walls.

In a series of children or young adults, we have observed types of hearts which we arbitrarily have termed over active hearts. In one type, we find marked pulsation of the aorta on fluoroscopic examination and some bulge of the aorta arch on films (Fig. 4*a*) In the other type, there is marked bulge of the pulmonary artery on fluoroscopic examination and bulge of the pulmonary area by film (Fig. 4*b*). Clinically, the overactive heart with an abrupt first sound and an accentuated pulmonic second sound simulates at times mitral stenosis. Bulging of the pulmonary artery in mitral stenosis usually occurs in advanced stages of rheumatic heart disease. It seems that the type showing increased aortic pressure, as demonstrated by pulsation and contour of the aorta by film, is part of hypertension in children, and the type related to the pulmonary or venous circulation, part of an increased pressure tension in the venous side of the circulation, which seems to occur in the child without demonstrable cardiac disease as a basis. Some of our blood-pressure determinations in children show arterial hypertension according to the standards set by Faber.[14] Such overactive hearts, we feel, should be studied for evidence of disease or disturbance of function elsewhere. We have found left and right axis deviation respectively, in the electrocardiographic records in some of these overactive hearts without demonstrable cardiac disease.

We will now discuss our findings under the individual abnormal cardiovascular conditions.

Hypertension. In hypertension in the adult, we do not believe there is a characteristic silhouette by Roentgen ray (Fig. 4*c*). Hypertension can be suspected by the marked pulsation seen over the entire cardiac and aortic field. Chronic hypertension shows

left ventricular hypertrophy and left axis deviation by electrocardiographic study. Simple hypertension or "early essential hypertension" with normal arterial walls gives more than normal pulsation with some dilatation of the aorta, which shows by film as a symmetrical accentuation of the normal aortic silhouette. Later, the silhouette is modified by sclerosis or other fibrotic changes.

Mitral Disease. In definite early mitral disease, the Roentgen ray findings may be normal (Fig. 5*c*). Progressive mitral disease shows hypertrophy of the left ventricle (Fig. 6*a*, *b*). However, since hypertrophy of the left ventricle is the only change noted in the cardiac silhouette in cases of uncomplicated mitral regurgitation, and since other etiologic factors can be responsible for such hypertrophy, this form of mitral disease cannot be diagnosed from the Roentgen ray outline alone. With well-marked mitral regurgitation, some stenosis of the mitral valve is also present. This is probably the cause of the more or less straight border from the base of the pulmonary artery to the apex of the heart, due to definite auricular hypertrophy (Fig. 7*a*). Where stenosis is the predominating lesion, there is definite bulging of the left auricle in addition to ventricular hypertrophy (Fig. 7*b*). The cardiac silhouette of mitral stenosis and regurgitation with definite enlargement over the pulmonary area must be differentiated from that of other conditions associated with increased pressure in the pulmonary artery with dilatation of the artery, as in patent ductus arteriosus, from conditions of increased pressure in the right heart with hypertrophy of the conus of the right ventricle,[15] and from conditions of pulmonary stenosis, congenital or acquired with right ventricular hypertrophy (Fig. 7*c*). Here, again clinical evidence is necessary to diagnose the pathologic condition and to interpret the Roentgen ray findings.

When we see, in children, during and after acute rheumatic fever, more than normal pulsation of the pulmonary artery and hear a systolic murmur at the pulmonary area, we are forced to the feeling that the pulmonary valves and artery are frequently involved in endocarditis and that acquired pulmonary stenosis may develop much the same as mitral stenosis does and frequently accompanies it. Occasionally, in well-marked mitral stenosis, when the disease is actively progressing, there is a blowing diastolic murmur over the pulmonary artery which may be inconstant due to dilatation of the pulmonary artery,[16] and fluoroscopically, there is more than usual pulsation of the artery and bulge of the pulmonary area by film. This type of mitral stenosis is most distressing (Fig. 8*a*, *b*, *c*, *d*, *e*) and indicates marked and long cardiovascular strain.[17] The case from which this illustration was obtained also showed progressive right-axis deviation in the electrocardiogram and increased voltage of the *T* wave (Fig. 9*a*, *b*, *c*, *d*, *e*). We have observed the same type of murmur, "the Graham Steel murmur,"[18] in an adult with actively progressing mitral disease of the regurgitant type, with the presence

also of an aortic diastolic murmur (Fig. 10*a*, *b*, *c*, *d*, *e*). This patient showed a collapsing type of pulse and electrocardiographic changes (Fig. 11*a*, *b*, *c*, *d*, *e*, *f*). One of our cases had clinical signs of tricuspid regurgitation with mitral stenosis and regurgitation (Fig. 7*d*), bulging of the pulmonary area in the film and an accenuated pulmonic second sound heard clinically. We detected no clinical signs of pulmonary regurgitation.

Pericarditis. The differential diagnosis of pericarditis[19] with effusion must be made from mediastinal tumors, pleural effusion and right- and left-sided hypertrophy in mitral and tricuspid regurgitation (Fig. 12). The clinical history of acute pericarditis is definite and the clinical signs are evident. With effusion, on fluoroscopic examination, we note a more or less globular contour of the heart, absence of differential pulsations of the various arcs of the cardiac silhouette and a waving characteristic movement of the heart shadow. Lateral views may show a convex outline of the pericardial reflection to the dome of the diaphragm instead of a concave one as is normally seem (Pendergrass).

In chronic adhesive pericarditis, the lack of mobility of the apex is visualized on fluoroscopic examination and the heart does not show the normal shadow separating from the shadow of the diaphragm on inspiration. Films occasionally show deformity of the pleuropericardial diaphragmatic shadows and it is probably because of these adhesions that many pleuropericardial friction sounds are heard clinically. The fluoroscopic study helps to explain the low and fixed position of the apex seen particularly in mitral stenosis accompanied by pericarditis.

Aortic Insufficiency. In aortic regurgitation due to syphilis, there is usually considerable deflection of the aorta as a whole with each systole (Fig. 13*a*, *b*). This left-sided swing of the aorta as a whole is the result of a high pulse pressure, systolic thrust and a marked diastolic recoil due to rapid changes in blood pressure or to actual blood regurgitation, within walls more or less damaged by disease and hyperfunction. We find commonly an associated aortitis which is readily diagnosed by films. We note a typical shadow to the left of the upper mediastinum below the horizontal arch, which extends from the shadow of the arch to the base of the left auricle (Fig. 13*a*). This shadow we have observed only in cases of aortitis and it is probably due to aortitis with dilatation of the descending aorta. Often this shadow seems to merge with that of the lower border of the arch and it obscures the pulmonary artery and the auricle on fluoroscopic examination and film and it is sometimes difficult to exclude an aneurysm (Fig. 13*a*). Differentiation is always possible however on fluoroscopic examination since in aortitis if the patient is turned from the anterior-posterior position into the right oblique position, the shadow cast by the dilated descending aorta can be made to disappear so that the horizontal arch with the left border of

the heart can be clearly traced. If aneurysm is present the silhouette of the arch is obliterated. This shadow of aortitis is additional evidence of the value of Roentgen ray in differentiating the causes of aortic regurgitation, as we never observe the shadow of aortitis in cases of uncomplicated rheumatic origin (Fig. 13*c*).

Congenital Heart Lesions. We do not believe there is a characteristic silhouette by Roentgen ray for any one type of congenital heart disease.[20] In patent ductus arteriosus, congenital heart disease of the noncyanotic type or type "cyanosis tardive,"[21] a characteristic and marked pulsation in the region of the pulmonary artery seen on fluoroscopic examination, in the presence of a palpable thrill and a marked systolic of a machinery murmur in a corresponding area of dullness in the third interspace to the left of the sternum, is presumptive evidence of this congenital anomaly. One of our cases of patent ductus shows a normal silhouette by Roentgen ray, a normal electrocardiogram, and a marked pulsation over the pulmonary area on fluoroscopic examination. There was a marked systolic murmur (heart sounds record gave the pitch of the murmur as 260 vibrations per second), a palpable thrill, no cyanosis and no dyspnea, and the first and second heart sounds were present and normal (Fig. 14*a*). We usually find marked bulging over the pulmonary area in patent ductus (Fig. 14*b*), due to a left to right shunt of the blood stream. This case had a marked systolic murmur, a palpable thrill to the left of the sternum in the third interspace, no cyanosis nor dyspnea. There was, on fluoroscopic examination, marked pulsation of the pulmonary artery. In cases of patent ductus in conjunction with a septal defect, we usually find marked bulging over the pulmonary area, probably due to blood-pressure changes in the right heart because of a left to right shunt of the blood stream due to the septal defect and to increased bloodflow through the patent ductus due to both of these factors. This case had two murmurs of different pitch and origin, one due to the ductus, which was transmitted upward to the left clavicle, and the other due to the septal defect, which was most marked over the sternum and was transmitted equally in this area (Fig. 14*c*).

In the presence of a prolonged systolic murmur, thrill in the third interspace to the left of the sternum, history of cyanosis from birth, oxygen unsaturation,[23] high red cell count, right axis deviation in the electrocardiogram,[24] and an absence of other murmurs, we have made a diagnosis of pulmonary stenosis, congenital in origin (Fig. 14*d*). This case had, in addition to right axis deviation in the electrocardiogram, unusually high voltage of the *T* wave. The second case (Fig. 14*e*) which we diagnosed as pulmonary stenosis, congenital in origin, proved on autopsy, to have also a septal defect, which probably accounts for the more or less globular type of heart and for the marked difference in the two electrocardiographic records in the two cases (Fig. 15*a*, *b*).

We have not found the marked bulging over the pulmonary area in congenital pulmonary stenosis, particularly when complicated by a septal defect. It may be that the gradual development of the circulatory mechanism in pulmonary stenosis congenital in origin, modifies the hypertrophy of the ventricle and adapts it to the added strain due to stenosis of the artery and interference with the circulation. We do find marked bulging over the pulmonary area in acquired pulmonary stenosis (Fig. 7*c*) and, at times in patent ductus. One of our cases (Fig. 14*f*) suggested acquired pulmonary stenosis or patent ductus. There was evidence of mitral endocarditis, left axis deviation in the electrocardiographic record and a history of rheumatic infection. The fluoroscopic examination suggested patent ductus by the marked pulsation seen over the pulmonary area. We felt, however, that the evidence made acquired pulmonary stenosis the correct diagnosis. Only the most careful cross checking of Roentgen ray and clinical findings is of value.

Aneurysm. The study of cardiac aneurysm antedates study of Roentgen ray by seventy years or more. The older writers give stress and strain, in the presence of weak muscle walls, as a causative factor. Morris[25] and others have shown that coronary artery disease and occlusion are paramount in the causation of aneurysms of the heart. Stress and strain were factors in 2 of the 3 cases of our series. Without fluoroscopic examination, the clinical findings in these cases of aneurysm of the heart could not have been interpreted. In the first case of our series, congenital heart disease was diagnosed from the clinical signs of a systolic murmur heard over the aortic area and midsternum, transmitted to both subclavian arteries, not heard in the carotids, a palpable thrill over the aortic area, presence of first and second sounds at the apex and to right of the sternum in the fourth interspace. There was, what seemed to be a palpable apex beat to the right and left of the sternum. There was cyanosis and dyspnea on exertion and a history of pertussis of severe type. Roentgen ray film showed a bulge to the right side of the heart, extending beyond the limits of the border of the right auricle. Fluoroscopic examination showed the pulsation to be synchronous with that of the left ventricle. Diagnosis was made of septal defect between the aorta and the base of the right ventricle and aneurysm of the right ventricle. (Fig. 16*a*)

The second of our cases of aneurysm of the heart presented the clinical signs of a systolic murmur over the pulmonary artery and a thrill characteristic of pulmonary stenosis. There was no cyanosis. Fluoroscopic examination showed a circumscribed shadow to the left of the upper area of the heart which had some pulsation not as marked as is usually seen in aneurysm of the heart or aorta. It was rather evident clinically that a mass pressing from behind on the pulmonary artery could give the signs present of pulmonary stenosis. A roentgen diagnosis was made of aneurysm or neoplasm (Fig. 16*b*). Autopsy (38608) showed aneurysm of the left ventricle,

congenital in origin, clot formation with possible pressure on the pulmonary artery.

Diagnosis of acquired aneurysm of the right auricle was made in the third case of this series, from the fluoroscopic study of the pulsation of a mass to the right of the heart. This man gave a history of severe cough with expectoration for two years. It was evident by fluoroscope that the time of the pulsation of the mass preceded systole of the ventricle. The fluoroscopic and film study showed the circumscribed shadow to be situated anteriorly, superimposed on the upper portion of the right auricle. With enlargement of the heart, time of pulsation of the mass and a history of strain, a diagnosis was made of aneurysm of the right auricle, acquired in type. This man has auricular fibrillation, mitral regurgitation and a history of purpura hemorrhagica. (Fig. 16*c*)

Aneurysms of the aorta or other vessels are less difficult in clinical diagnosis. Increased supracardiac dullness, relative blood pressure changes in arms, and in arms and legs, bruits and murmurs over the course of bloodvessels, pulsating masses in the course of arteries, history of syphilis and differential pulsations under fluoroscopic study usually make the diagnosis evident (Fig. 17*b*, *c*).

Arterial Sclerosis. By fluoroscopic and Roentgen ray film examination, we suspect the existence of arterial sclerosis by an upward tilting of the silhouette of the horizontal arch of the aorta, the mechanism of which has been suggested in connection with hypertension (Fig. 17*a*). The width of the normal aorta is measured by lines parallel with the long axis of the body of the sixth dorsal vertebra. In arterial sclerosis, the arch of the aorta is displaced upward and inward, due to the tortuosity, dilatation and rotation of the aorta caused by an upward thrust exerted by the blood stream on sclerotic walls which lack normal resiliency. The apparent diameter is therefore altered from a horizontal to an oblique line, which makes an angle of approximately 45 degrees with the transverse line paralleling the long axis of the sixth dorsal vertebra. By clinical examination, we, at times, detect atheroma of vessel walls by the murmurs or bruits heard over the vessels. Roentgen ray at times demonstrates atheromatous walls, which may be clearly and definitely visualized (Fig. 17*b*, *c*). The electrocardiogram gives evidence at times of fibrotic changes in the heart muscle or conduction system. The presence of sclerotic changes in the eye grounds is additional evidence of cardiovascular sclerosis, and with hypertension, helps to correlate the clinical and Roentgen ray findings in the diagnosis of arterial sclerosis.

Summary. One hundred cases of congenital and acquired heart disease have been studied by clinical, electrocardiographic, clinicopathologic and Roentgen ray laboratory methods. We have accepted as normal hearts those without clinical signs or symptoms of disease, and which by Roentgen ray show no hypertrophy, have normal respiratory movements, no unusual pulsations of the

various cardiac areas, particularly of the aortic and pulmonary areas, and which show no axis deviation, arrhythmias nor changes in the conduction system by electrocardiographic examination.

The heart in the obese (5 cases), while normal from clinical examination, usually showed increased measurements on deep inspiration, which we believe is due to an anterior rotation of the heart. The electrocardiogram showed left axis deviation in those showing anterior rotation. All five cases of obesity had dyspnea on exertion. A possible explanation of the dyspnea may be an anatomic one due to anterior rotation or lack of normal rotation with torsion and mechanical pressure on the great vessels and mechanical interference with the circulation. We believe the obese heart is abnormal in physiology, even if not the seat of pathologic changes in structure.

In children and young adults (7 cases), we have found a type of heart without clinical evidence of disease which we have called overactive. Two of the 7 cases showed hypertension and increased pulsation of the aorta by fluoroscopic examination and bulge of the aorta by film. Five of the cases showed marked pulsation of the pulmonary artery and bulge of the pulmonary area by film. One case showed left axis deviation in the electrocardiogram and one case right axis deviation. We feel that such hearts should be studied for evidence of disease elsewhere.

Hypertension in the adult (12 cases) showed marked pulsation of the whole cardiac field, particularly of the aorta. The silhouette of the aorta varied from the symmetrical bulge due to high sustained pulse pressure and dilatation of normal arterial walls to the type modified by arterial sclerosis in which the arch has an upward tilt.

In rheumatic heart disease primarily involving the mitral valve (43 cases), 7 were diagnosed as mitral stenosis with the "inspiratory type" of heart; 21 as mitral regurgitation with some stenosis of the mitral valve and 12 as mitral regurgitation with definite stenosis evident by clinical signs. Three cases were questionable for endocardial disease. Marked pulsation over the left auricle and an inspiratory type of heart were interpreted as evidence of stenosis by Roentgen ray examination. One of the mitral cases had pericarditis with effusion.

In aortic regurgitation of rheumatic etiology (5 cases) one showed endocarditis also of the mitral valve, a Streptococcus viridans infection with ulceration through the aortic to the mitral. This case showed a marked acidosis at times (pH 7.22 to 7.28) edema of the subcutaneous tissues and pain, particularly aortic in origin. In aortic regurgitation of syphilitic origin (10 cases) 4 cases showed the shadow of aortitis. The silhouette of the arch showed definite swing of the aorta to the left due to a high pulse pressure unsustained in the presence of weak or diseased arterial walls. Both the shadow of aortitis and the definite swing of the aorta to the left were absent in aortic regurgitation due to rheumatic infection.

In congenital heart disease (8 cases) we found no silhouette

characteristic of any one type of this kind of heart disease. The origin and transmission of murmurs, differential blood pressures, the presence or absence of cyanosis, hypertrophy of the various areas of the heart and the history were cross-checked by electrocardiographic evidence of axis deviation and voltage of the *T*-wave and Roentgen ray study of the pulmonary area. Septal defects give a more or less globular-shaped heart and in the two cases of undoubted pulmonary stenosis, one of which had a septal defect, electrocardiographic records show contrasting features which need further explanation.

Three cases of aneurysms of the heart were studied: one of the right ventricle with a septal defect between the aorta and the base of the right ventricle, and one of the left ventricle, both congenital in origin. These cases gave evidence of congenital defects by murmurs, heart sounds and by Roentgen ray examination. Pulsations of the abnormal masses were timed by fluoroscopic examination and the masses demonstrated by film. The aneurysm of the right auricle, the third of this series, gave no clinical evidence by murmurs.

Aneurysms of the aorta (4 cases) were diagnosed clinically and confirmed by fluoroscope and film. One case died in uremia and autopsy showed the whole heart and aneurysm bound to the surrounding tissues by adhesions in a process of repair. It could never have ruptured.

Arterial sclerosis (3 cases) showed by Roentgen ray a type of heart characterized by an upward tilting of the horizontal arch of the aorta and an oblique diameter of the arch. At times, sclerosis was evident by calcification of the vessel walls. The electrocardiogram is of value in the diagnosis of fibrotic changes in the cardiovascular system and the eye grounds always showed evidence of arterial changes.

In this small series of cases, sex does not seem to be of any importance. Age is an interesting factor in the overactive type of heart in childhood and early adolescence. We have included in our study a case of a woman one hundred years of age whose clinical and laboratory tests were normal. The peripheral capillary circulation showed marked changes due to senility and the patient had a marked sensitivity to temperature changes, particularly to cold. The height and weight ratio were important only in the definitely obese, all of whom gave clinical symptoms. Two of the 43 rheumatic heart cases had positive Wassermann tests and 2 of the 10 hypertension cases also not showing valvular lesions or aortitis. Tachycardia was a factor in the overactive hearts and 12 of the 43 cases of rheumatic heart disease had heart rates over 100. Four of the 100 cases showed definite renal involvement with high diastolic pressures, albumin in the urine and high specific gravity. Anemia was a factor in 3 of the 7 cases of overactive hearts and in 5 of the rheumatic hearts. Forty-two of the 43 cases of rheumatic heart disease gave a history of rheumatic infection: 21 of acute rheumatic fever, 15 of tonsillitis and 16 of focal infection. Thirty-four of these

43 cases of rheumatic heart disease had respiratory infections as measles, pneumonia, bronchitis or pertussis. Seventy-four of the 100 cases studied had a history of the above respiratory infections which seems probably the most important clinical result of this study of cardiac or cardiovascular disease. Three of the hypertension cases had had typhoid fever. Fourteen of the 100 cases had normal electrocardiograms and all but the 2 normal cases included, had respiratory symptoms. Fifty-eight of the entire series showed definite eye-ground changes.

Conclusions. We believe that Roentgen ray study helps to demonstrates the functional efficiency of the heart in respiration, the degree of pulsation and relative changes in the various areas of the heart and vessel walls, and that the classification of hearts that are not normal as inspiratory in type or expiratory in type is explanatory and a functional classification of value, based on physiologic study of normal and abnormal hearts.

The heart in the obese is abnormal in physiology, even if not the seat of pathological changes in structure.

The overactive heart is an entity demonstrated by Roentgen ray and confirmed by clinical examination.

Roentgen ray is of value in the diagnosis of hypertension and of mitral disease and in the clinical differentiation of functional from organic heart disease.

We feel that the study of the pulmonary area is worth while in the decision between functional and organic heart disease; that it explains the physical signs as to murmurs, dilatation, and palpable thrills at the pulmonary area; that some of these signs may be due to hypertrophy of the conus of the right ventricle or dilatation or stenosis of the pulmonary artery; that such study is valuable in the diagnosis of pulmonary stenosis and regurgitation and in the clinical differentiation of diseases of the pulmonary and aortic valves where a diastolic murmur is heard at the base of the heart, particularly where the lesion of mitral regurgitation and stenosis is present; that patent ductus cannot be adequately diagnosed without fluoroscopic study; and that all murmurs at the pulmonary area need explanation in terms of definite pathology or disturbance of function.

As is well known, Roentgen ray furnishes additional evidence of pericarditis with effusion and of adhesive pericarditis. The fluoroscopic examination shows the fixed and low position of the apex, particularly in cases of mitral stenosis.

We have nothing new to add to the previous work in the differentiation of the causes of aortic regurgitation, except the possible value of the additional shadow of aortitis of the descending aorta as evidence of aortic regurgitation of syphilitic rather than of rheumatic origin.

Aneurysms are best demonstrated by fluoroscopic examination and the differentiation from other thoracic masses is only possible at times by this method.

Roentgen ray demonstrates arterial sclerosis by a characteristic silhouette of the heart and great vessels, and by the presence at times of atheroma and calcification of vessel walls.

We believe that the rôle of respiratory infections in heart disease is the most important clinical deduction from the present study.

BIBLIOGRAPHY.

1. Zinn, W.: Zur Diagnose der Persistenz des Ductus Botalli, Berl. klin. Wchnschr., 1898, **35**, 433.

2. Groedel, F. M.: Rœntgendiagnostic in der inneren Med., München, F. Lehmans Verlag, 1924, **1**, 349.

3. Assmann, H.: Die Klinische Rœntgendiagnostic der inneren Erkrankungen, 3d ed., 1925, p. 82.

4. Vaquez, H., and Bordet, E.: The Heart and the Aorta: Studies in Clinical Radiology, New Haven, Yale University Press, 1920; English translation from 2d ed. by James Honeij and John Macy.

5. McPhedran, F. M., and Weyl, C. N.: Automatic Synchronization of *X*-ray Exposures, Am. J. Med. Sci., 1925, **169**, 510; The Application of Automatic Synchronization of Roentgen Ray Exposures to the Study of Intrathoracic Movement, Proc. Am. Phil. Soc., 1925, **64**, 90.

6. Ledbetter, P. V., Holmes, G. W., and White, P. D.: The Value of *X*-ray in Determining the Causes of Aortic Regurgitation, Am. Heart J., 1925, **1**, 3.

7. Abreu, de M.: Essai sur une nouvelle Radiologie Vasculaire, Paris, Maison & Cie, 1927, p. 58.

8. Pendergrass, E. P.: The Value of an *X*-ray Examination in the Interpretation of Heart Lesions, Med. Clin. North America, Heart, 1927, **10**, 1513.

9. Le Wald, L. T., and Turvell, G. H.: The Aviator's Heart, Roentgen Ray Studies under Conditions Simulating High Altitudes, Am. J. Roentgenol., 1920, **7**, 67.

10. Henderson, Yandell, Whitney, James, L., *et al.*: Medical Studies in Aviation, J. Am. Med. Assn., 1918, **71**, 1383.

11. Campbell, J. M. H.: The Effect of Exercise on the Respiratory Exchange in Heart Disease, Guy's Hospital Report, 1926, **76**, 394.

12. Wagoner, G. W.: Studies on Intraäbdominal Pressure, Am. J. Med. Sci., 1926, **171**, 697.

13. Groedel, F. M.: Die physikalische Therapie der Herz Gefässe und Zirkulationsstorungen, Berlin, J. Springer, 1925, p. 5.

14. Faber, H. K., and James, C. A.: Range and Distribution of Blood Pressures in Normal Children, Am. J. Dis. Child., 1921, **22**, 7.

15. Wessler, H., and Jaches, L.: Clinical Roentgenology of Diseases of the Chest, Troy, N. Y., Southworth Co. 1923, p. 24.

16. Schwartz, S. P.: The Radiological Signs of Pulmonary Insufficiency, Am. Heart J., April, 1927, p. 407.

17. Sailer, J.: Relative Pulmonary Insufficiency (Graham Steele Murmur), Am. J. Med. Sci., 1915, **150**, 502.

18. Steele, G.: Medical Chronicles, Manchester, 1906, p. 1105.

19. McPhedran, A.: Diseases of the Respiratory System, Osler and McCrae, Modern Medicine, 1927, **4**, 365.

20. Abbott, M., and Dawson, W. T.: The Clinical Classification of Congenital Cardiac Disease with Remarks upon its Pathological Anatomy, Diagnosis and Treatment, Int. Clin. Am., 1924, **34**, 156.

21. Abbott, M. E.: Congenital Heart Disease, Osler and McCrae, Modern Medicine, 1927, **4**, 512.

22. Boothby, W. N., and Abbott, M. E.: On the Venous Blood as a Diagnostic Sign in Cardiac Defects, Bull. Assn. Med. Mus., Ann Arbor, 1916, **6**, 122.

23. Goldschmidt, S., and Light, A. B.: A Method of Obtaining from Veins Blood Similar to Arterial Blood in Gaseous Content, J. Biol. Chem., 1925, **64**, 57.

24. McCulloch, H.: Electrocardiographic Studies of Congenital Heart Disease, Am. J. Dis. Child., 1916, **12**, 30.

25. Morris, L. M.: Cardiac Aneurysms, Am. Heart J., 1927, **2**, 548.

26. Abbott, M. E.: Contributions to Medical and Biological Research, New York, P. B. Hoeber, 1919, **2**, 899.

THE EFFECT OF AMYTAL ANESTHESIA UPON THE UTERUS AND ITS USE IN OBSTETRICS.

By D. L. Drabkin, M.D.,
INSTRUCTOR IN PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF PENNSYLVANIA,

I. S. Ravdin, M.D.,
PROFESSOR OF RESEARCH SURGERY, UNIVERSITY OF PENNSYLVANIA,
AND
J. C. Hirst, M.D.,
ASSISTANT PROFESSOR OF OBSTETRICS, UNIVERSITY OF PENNSYLVANIA,
WITH THE COLLABORATION OF
M. E. Lapham, M.D.,
RESIDENT IN OBSTETRICS, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA.

(From the Departments of Physiological Chemistry, Research Surgery and Obstetrics, School of Medicine, University of Pennsylvania.)

The claims which have been brought forth for the therapeutic superiority of each of many derivatives of barbituric acid since the original synthesis of barbital by Fischer and Dilthey[1] may well be doubted.[2] One of these derivatives, "amytal" (iso-amyl-ethyl-barbituric acid) was synthetized in 1923 by Shonle and Moment.[3] From the time of its physiologic introduction by Page[4] amytal has become increasingly popular as a safe and effective anesthetic for animal experimentation. It is thought to possess several negative characteristics, if not virtues, as an anesthetic. When administered to dogs, it does not affect the blood-sugar level,[4, 5, 7] blood concentration,[6] metabolic rate,[7, 8] or blood pH and CO_2 combining power.[9] The most discouraging feature in the use of this compound has been a variability in the solubility and anesthetic potency of the product. This factor in itself was sufficient justification for the exclusion of amytal from "New and Nonofficial Remedies." Furthermore, nothing is known concerning the fate of this substance in the organism. In spite of such significant objections, amytal has been "tried out" on man with apparent impunity.[10, 11] Two years ago, apparently for the first time in this country, one of us had the opportunity to employ amytal anesthesia in human subjects. In this work, the administration of the anesthetic *per rectum* was found very effective.[12]

The peculiar state of hypnosis, resembling "anergic apathy" and the prolonged stupor, characteristically present in dogs given small doses, suggested the possibility that this anesthetic might prove of value in obstetrics. With this aim in view, during the past year the writers have collected data which they feel merit a preliminary report at this time.

Experimental. Kymographic records of the contractions of the uteri of virgin guinea pigs were made. In some cases the uteri were studied *in situ* in animals anesthetized with large doses of amytal. In other cases one cornu of the uterus was removed from the animal and studied in a constant temperature bath (Dale) to which high concentrations of amytal were added. In all instances, the rhythmic contractions were maintained under the anesthetic. The response of the uteri to the oxytocic principle of the pituitary (Parke, Davis & Co.) was not disturbed after amytal anesthesia.

Albino rats, weighing about 200 gm., have been found very suitable for the biologic assay or standardization of the amytal preparations. With two preparations of good anesthetic potency, the average dose and time relationships were as shown in the accompanying table:

Mgm. amytal per kilo body weight.	25	50	75	100	150	200
Time in minutes for onset of complete anesthesia . .	Incomplete	4–4½	3	2–2½	1½	1½

The amytal was injected intraperitoneally and the speed of onset of anesthesia in this species was noteworthy. In comparison with dogs, recovery from nonfatal doses was also relatively rapid in rats. About 30 per cent of the rats receiving 150 mg. per kilo body weight and about 60 per cent of those given 200 mg. per kilo died. In rats, therefore, the ratio of the anesthetic dose (50 mg. per kilo) to the fatal dose was somewhat less than 1 to 3. Other preparations of amytal have been assayed by this procedure and found appreciably less potent anesthetically and more toxic than the above. The writers, therefore, consider the "standardization" of the preparations to be administered to patients of prime importance.

Amytal has been used for anesthesia in 33 obstetrical patients. The dosage in the first 30 cases was 25 mg. per kilo of "assayed" preparations given by rectum. In the last 3 cases, the dosage has been 30 mg. per kilo. The advantages of the rectal administration of the drug are threefold: (1) The patient receives the drug believing she is being given an "enema." This permits of nearly a perfect anoci technique. (2) The patient goes to sleep slowly, complete relaxation occurring in from thirty to forty-five minutes. (3) No precautions need be taken in regard to colloidal material in the solution since this presumably makes no difference in the intestinal tract, but is a matter of serious importance in intravenous injection.

Results. In 13 cases the result was excellent. By this we mean complete anesthesia throughout the period of delivery. The patients were quiet, apparently in deep sleep, but uterine contractions continued. In 10 cases, the results were classified as good. These patients moaned or moved somewhat during uterine con-

tractions, but between pains were quiet and relaxed. In 7, the results were fair. The patients were quiet, on the whole, between pains, but were noisy and unmanageable during pains. All patients in this group were restrained. Two patients were grouped under poor results. In both of these the uterine contractions disappeared while the patients were under anesthesia and did not begin again until complete recovery from the effect of the amytal. It should be remembered that the disappearance of labor pains after they have begun is not unusual in unanesthetized patients so that the cessation of uterine contractions may not have been due to the amytal.

In the majority of patients, no change took place in the systolic or diastolic blood pressure throughout the period of anesthesia. A drop of over 10 mm. of mercury was taken as definite evidence of an alteration in the blood pressure. This occurred in 5 patients. The maximum drop was 50 mm. When the pressure is high from fright or excitement prior to the administration of amytal, it tends to drop to a normal level as the patient goes to sleep.

The temperature showed very little if any variation and the drop in temperature noted in many animals during amytal narcosis was not observed in these human subjects.

The pulse rate of the patient remained stationary in about one-half of the cases and was raised in the other half. The maximum rise was 30 per minute and this occurred during the period when the head came down on the pelvic floor. The fetal heart rate was unaltered in every patient under anesthesia.

The respiratory rate was rarely affected. In 4 cases it was increased, but in no instance did we observe the very slow respirations which frequently occur after the intraperitoneal administration of the drug to the dog.

The force of the uterine contractions was diminished in 2 patients who subsequently delivered while under anesthesia and completely ceased in 2 patients who recovered from the effect of the drug and were subsequently delivered.

Outlet forceps or high forceps were used or version practised in 17 cases. In 4 of these supplemental anesthesia was used because the patients were apparently in pain although they did not remember having had pain when they finally recovered from the anesthesia.

Two babies were slightly asphyxiated. Both of these were in difficult deliveries. In the remainder the babies cried lustily when born. They were not narcotised nor did they show any other effect of the drug.

The period of sleep from inception to completion of anesthesia varied. In 18 of the cases where careful records were kept, 1 patient was completely awake in six hours, 6 recovered within twelve hours, 5 in eighteen hours, and 6 in twenty-four hours.

Mortality. There was one baby born dead in this series. This occurred twenty-seven hours after the administration of the amytal

and at a time when the patient was completely recovered from the effect of the drug. The baby's fetal heart rate was 128 throughout the period of anesthesia. Six hours after recovery from the drug and after a prolonged labor, high forceps were applied. The child was dead when delivered. Though the cause of death has not been definitely ascertained, this has been classified as an amytal death. The mothers all recovered.

The most striking phenomenon was the amnesia which was characteristic of these cases. Not one of the patients who slept remembered the delivery. Even the refractive individuals went to sleep after the birth of the child and upon awakening were loath to believe that the child had been born.

The dose of amytal used in these cases is one-half the anesthetic dose for the dog and rat. With the use of 30 to 35 mg. per kilo of body weight, we believe that even better results may be expected. The writers are particularly anxious, however, to leave the impression that it would be unwise and even dangerous to employ preparations of amytal on patients, unless these preparations have been tested as to potency and toxicity.

Summary and Conclusions. Iso-amyl-ethyl barbituric acid (amytal) was found to have no effect upon the rhythmic contractions of the virgin guinea pig's uterus either *in vitro* or *in vivo*. Furthermore, the uterus of animals anesthetized with this drug responded to the oxytoxic principle of the pituitary.

A method for the standardization of the amytal solutions has been introduced. The importance of such biologic assay has been pointed out.

The drug has been found to produce effective anesthesia in a large proportion of obstetrical cases. In all of them its administration resulted in a condition of amnesia, so that, after delivery and recovery from the drug, the patient had no recollection of the period of labor.

Very little, if any, effect was noted on the maternal pulse, temperature, or respiration. The blood pressure dropped in 5 of the 33 cases more than 10 mm. of mercury, but was well maintained in the remainder.

The babies at the time of delivery showed little, if any, effect of the drug.

A new method for the administration of the drug was presented which has been found effectual in both obstetrical and general surgical cases. The latter will form a separate communication.

BIBLIOGRAPHY.

1. Fischer, E., and Dilthey, A.: Ann. der Chem., 1904, **335**, 334.
2. Eddy, N. B.: J. Pharm. and Exper. Therap., 1928, **33**, 43; J. Am. Med. Assn., Editorial, 1928, **91**, 398.
3. Shonle, H. A., and Moment, A.: J. Am. Chem. Soc., 1923, **45**, 243.
4. Page, I. H.: J. Lab. and Clin. Med., 1923, **9**, 194.

5. Hepburn, J., Latchford, H. K., McCormick, N. A., and MacLeod, J. J. R.: Am. J. Physiol., 1924, **69**, 555.
6. Drabkin, D. L., and Edwards, D. J.: Am. J. Physiol., 1924, **69**, 177.
7. Deuel, H. J., Jr., Chambers, W., and Milhorat, A. T.: J. Biol. Chem., 1926, **69**, 249.
8. Drabkin, D. L.: J. Biol. Chem., 1927, **75**, 443.
9. Hines, H. M., Boyd, J. D., and Leese, C. E.: Am. J. Physiol., 1926, **76**, 293.
10. Zerfas, L. G., McCallum, J. T. C., Shonle, H. A., Swanson, E. E., Scott, J. P., and Clowes, G. H. A.: Proc. Soc. Exper. Biol. and Med., 1929, **26**, 399.
11. Zerfas, L. G., and McCallum, J. T. C.: J. Indiana State Med. Assn., 1929, **22**, 47.
12. Ravdin, I. S.: Unpublished data.

OBSERVATIONS ON CORONARY THROMBOSIS.

With a Report of Three Recovered Cases.

By A. Carlton Ernstene, M.D.,

formerly resident physician thorndike memorial laboratory boston city hospital; assistant in medicine beth israel hospital and assistant in medicine harvard medical school.

boston, mass.

(From the Thorndike Memorial Laboratory, Boston City Hospital and the Department of Medicine, Harvard Medical School.)

Although several excellent general reviews of coronary artery thrombosis are available, they contain reports of but few cases which have been observed over a long period of time. For this reason, it is felt that an account of 3 recovered patients studied for from one to about four years after the attack and of 6 other patients observed from soon after the occlusion until death may be of interest. All 9 patients were males; the youngest was fifty-five and the oldest seventy-three years of age. Arteriosclerosis was the principal cause of the occlusion in all. None gave evidence of syphilis or of rheumatic fever. Four patients had had no preceding cardiovascular symptoms. Five, however, had had dyspnea, with or without palpitation; and 4 of these also had had anginal seizures. In one instance there was moderate myocardial failure at the time of onset of thrombosis. One patient is known to have had auricular fibrillation for at least two years and another for at least six months before the occurrence of coronary occlusion. These 2 cases are unusual inasmuch as previous reports indicate that coronary thrombosis rarely occurs in a heart with fibrillating auricles. Necropsy was performed on 3 of the fatal cases.

In all patients the diagnosis was based primarily on the presence of characteristic symptoms and physical signs, substantiated by laboratory and electrocardiographic findings. The presenting symptom in all was sudden, excruciating, substernal, precordial,

or epigastric pain, with or without radiation, lasting from a few hours to several days and accompanied by severe dyspnea. Nausea, vomiting, and extreme weakness usually attended or closely followed the onset. Physical signs of myocardial weakness were always present on admission. The heart sounds usually were distant and of poor quality; and disturbances of rhythm were common, particularly premature beats, gallop rhythm, auricular fibrillation, and varying degrees of heart block. Sudden changes in rhythm, often of short duration, frequently were observed. Persistent moist râles at the bases of the lungs were constantly found. The initial blood pressure generally was low, and the pulse weak and rapid. Three patients seen soon after the attack appeared to be in profound shock with subnormal temperature and ashen, gray, cold, moist skin. Enlargement of the liver was noted in 3 instances, but only 2 patients had peripheral edema on admission. The onset in the patient with antecedent myocardial failure presented no unusual features. A pericardial friction rub was heard in only one case.

Although patients coming to the hospital within thirty-six hours from the time of the first symptoms attributable to thrombosis, as a rule, had a subnormal temperature on admission, fever between 99° and 101° F. usually developed within the next twenty-four to forty-eight hours and persisted for two to ten days. Leukocytosis of from 11,000 to 21,000 cells per c.mm. was present in 8 cases, generally appearing within thirty-six hours of the onset, and continuing, as a rule, for some time after the temperature had become normal.

The occurrence of embolic phenomena in coronary thrombosis has been emphasized by Hamman.[1] Two of the 9 patients of the present series raised a large amount of bloody sputum, one, two days and the other, twelve days after the occurrence of occlusion. In both, hemoptysis was followed by marked increase in the degree of cardiac failure. None of the other 7 patients gave evidence of embolism at any time, although 2 showed old infarcts of the spleen at necropsy and 1 of these had, in addition, a small pulmonary infarct. It is known that in cardiac failure infarction may occur in the pulmonary or greater circulation without producing evident symptoms.

Blood pressure was recorded frequently in all patients. Not uncommonly a progressive fall in the systolic level was noted for several days after the beginning of the attack. Subsequent clinical improvement was accompanied by a rise of varying degree, extending to a distinctly high level in 2 patients; while with the occurrence of further attacks or the development of severe cardiac failure there was invariably a further fall.

The vital capacity of the lungs was studied in 7 patients. All showed marked reduction below normal on admission to the hospital, and in 3 instances the initial reading was 1600 cc. or less. These

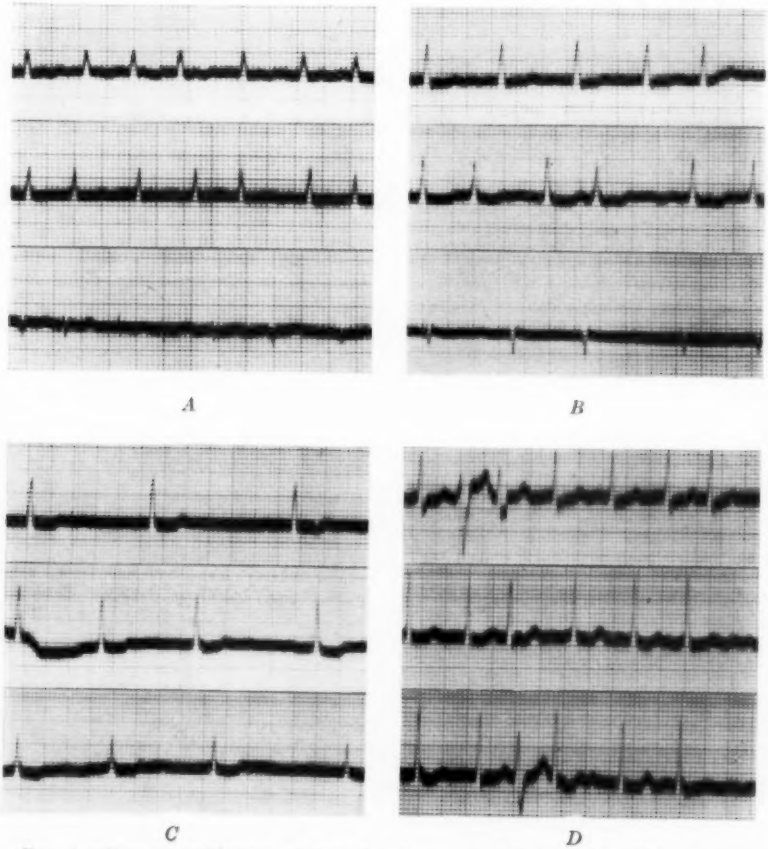


FIG. 1.—Electrocardiograms of Case I. *A*, record of October 15, 1924, ten days after onset of attack; *B*, record of October 17, 1924, showing increased amplitude of *Q-R-S* complexes; *C*, record of October 22, 1924; *D*, record of December 9, 1924.

UNIV OF MICH

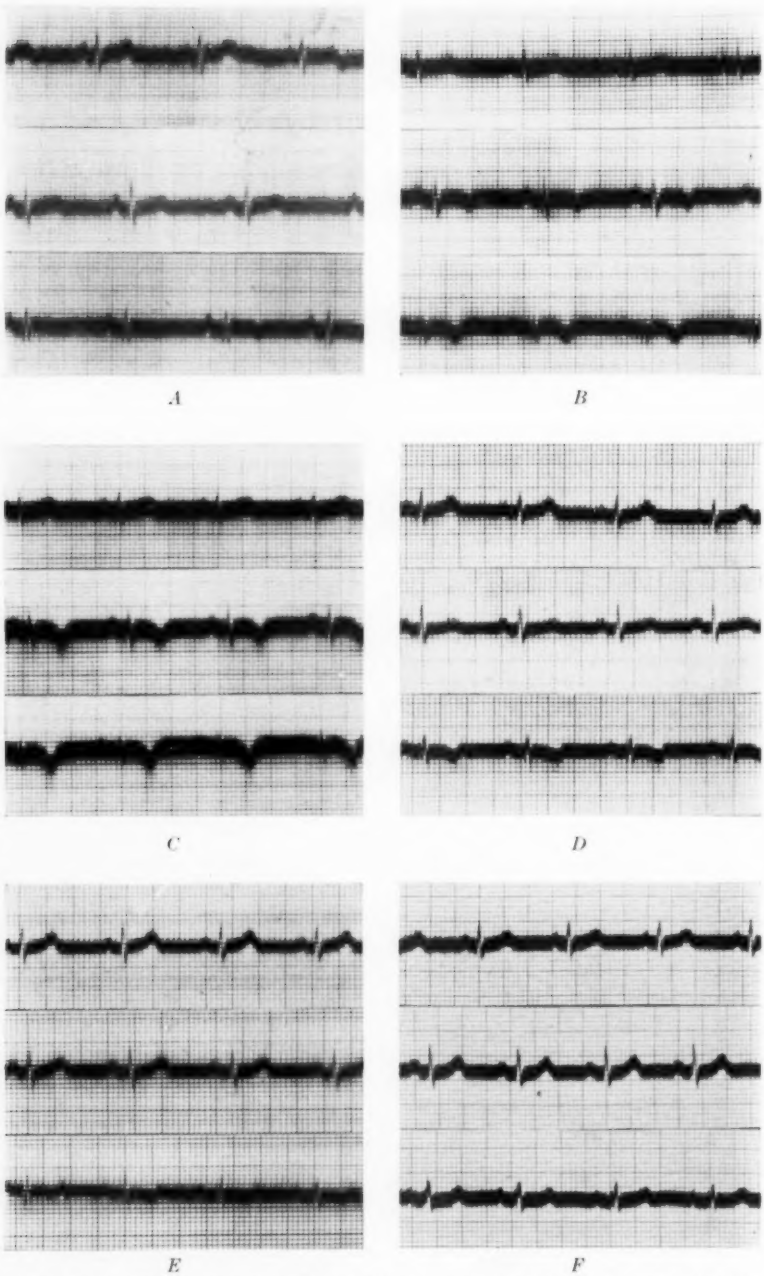


FIG. 2.—Electrocardiograms of Case II. *A*, record of March 2, 1926, the day after onset of attack; *B*, record of March 8, 1926, showing sharply-peaked negative *T* waves and upwardly convex *S-T* intervals in Leads II and III; *C*, record taken eight weeks after onset, showing *T* wave and *S-T* interval changes still present; *D*, record taken twelve weeks after onset, with *T*-2 upright and *T*-3 of diminished amplitude; *E*, record taken five months after attack, with *T*-3 diphasic; *F*, record one year after attack, with *T*-3 upright. Subsequent tracings show no further changes.

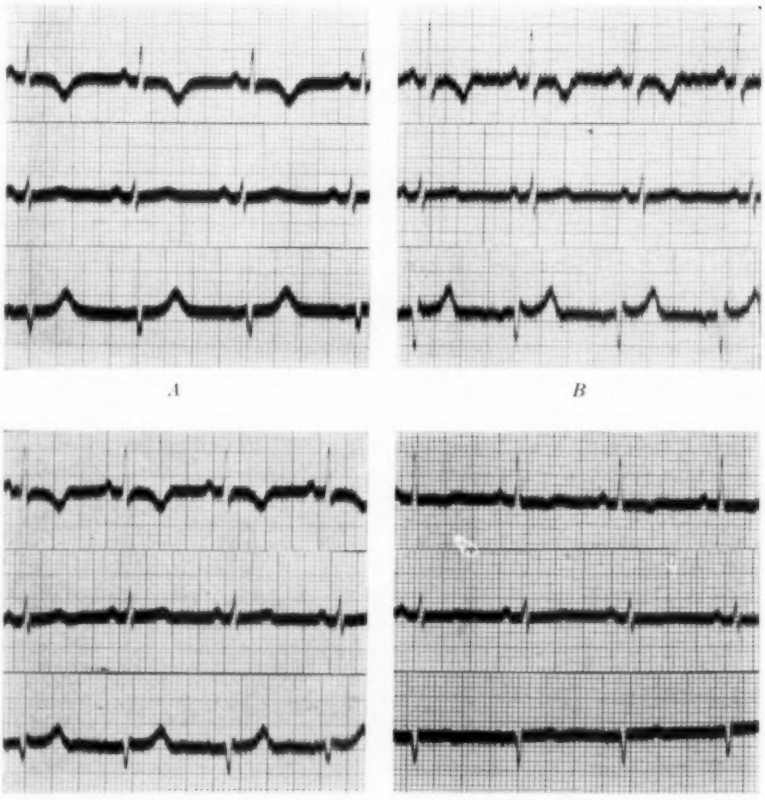


FIG. 3.—Electrocardiograms of Case III. *A*, record taken twenty-two days after onset of attack, showing coronary *T* wave in Lead I; *B*, record ten days later; *C*, record one week later; *D*, record taken three months after the attack; note the marked change in *T* wave in Leads I and III. Subsequent records show no further changes.

observations are of interest in view of the fact that so few peripheral signs of cardiac failure were present at the time. Clinical improvement usually was accompanied by an increase in vital capacity, while an unfavorable course was attended by further reduction.

Fluoroscopic Studies. Repeated fluoroscopic observations on the extent of cardiac excursion were made on 5 patients, 2 of whom recovered. In each instance the first examination was carried out within a few days of the onset and, without exception, showed marked diminution of cardiac pulsation. Two patients, one of whom recovered, presented only extremely slight, scarcely visible pulsations of the heart. The beats were so feeble indeed that the movements resembled a see-saw-like motion rather than true contractions. Subsequent examinations of patients who ultimately died showed no appreciable changes from the original findings, although in each instance there was temporary clinical improvement before the final decline. In the patients who recovered, however, there was a relatively rapid return of strong, visible, systolic pulsations coincident with clinical improvement, rising blood pressure, increased vital capacity, and improved quality of the heart sounds. Frothingham[2] has made similar observations on a patient who recovered.

Fluoroscopic examinations of the heart also were made on a number of patients with angina pectoris at a time when they were having no pain. Several of them, in whom the heart muscle obviously was very weak, showed definitely subnormal systolic pulsations. In none of these cases, however, did the diminution amount to the very faint see-saw movement observed in 2 of the patients with coronary thrombosis.

Electrocardiographic Studies. Electrocardiograms were taken on all the patients at frequent intervals. With one exception, the first record was always obtained within twenty-four hours of admission. Four patients had left ventricular predominance. All showed diminution in amplitude of the *Q-R-S* complexes accompanied, in many instances, by slurring, notching, or spreading. No relationship was observed between *Q-R-S* amplitude and changes in the clinical condition, blood pressure, vital capacity, or extent of cardiac excursion as observed fluoroscopically.

Each of the 6 fatal cases showed the *S-T* interval originating from a point on the *Q-R-S* complex above the isoelectric level, as described by Pardee.[3,4] Usually this feature was present in the initial record, although in one instance it did not appear until five days after the onset of symptoms. The upwardly convex *S-T* interval of Pardee[5] and the inverted, sharply-peaked *T* wave first described by Smith[6,7] were observed subsequently in 3 of these patients, the "coving" persisting, in each instance, for a variable time after this development.

An elevated origin of the *S-T* interval was not present in any

patient who recovered, but an upwardly convex *S-T* interval and negative, sharply-peaked *T* wave were observed in two (Figs. 2 and 3). In both instances these changes disappeared before the end of the third month.

Subsequent Attacks. Each of the 6 fatal cases showed on one or more occasions, without apparent cause, a sudden change in the clinical course. This usually consisted of recurrence or exacerbation of pain with sudden, conspicuous increase in dyspnea and other signs of myocardial failure. In the light of post mortem studies these sudden clinical alterations may be attributed either to extension of the existing thrombus or occurrence of fresh occlusion in another area. Of the 6 fatal cases, 4 died within three hours of onset of one of these episodes, and in the 3 with necropsy, the heart showed evidence of fresh and old infarction.

It is of interest that, in contrast to the fatal cases, 2 of 3 patients who recovered had no such attacks.

Report of Cases.—CASE I. J. R., a white male machinist, aged fifty-nine years, admitted October 15, 1924, complaining of epigastric and precordial pain, shortness of breath, and swelling of the lower extremities. For two years there had been dyspnea and palpitation on exertion with rather frequent attacks of angina pectoris. In May, 1924, the patient had been admitted with myocardial failure of *gradual* development, and at that time had auricular fibrillation. He improved rapidly with digitalis therapy and was discharged after five weeks. About October 1, 1924, he developed a severe, moderately productive cough with rapidly increasing dyspnea; and three days later, while doing light work, suddenly experienced severe, sharp, non-radiating epigastric and precordial pain with marked palpitation. With rest the pain quickly disappeared, but epigastric distress and a sense of abdominal distention persisted for over an hour. The following morning he attempted to finish his work, but in a few minutes the pain recurred with greatly increased intensity, accompanied by sudden, marked weakness, faintness, severe dyspnea, nausea and vomiting. Rest gave no relief. The pain persisted undiminished and became worse the next morning after a severe coughing spell with hemoptysis. Then after several hours, it diminished but did not entirely disappear during the ten days before admission to the hospital.

Examination showed a markedly orthopneic male in great distress. The skin was grayish; the lips were cyanotic, and the scleræ slightly icteric. The thorax was of the emphysematous type with signs of fluid at both bases. The vital capacity was 1700 cc. The left border of the heart was 12 cm. from the midline, and the apex impulse was neither seen nor felt. The heart sounds were very distant. No murmurs or friction rubs were heard. The apex rate was 154 per minute, absolutely irregular, with a pulse deficit of over 50. The radial arteries were moderately thickened. The blood pressure was 115 mm. systolic, 85 mm. diastolic. The liver extended 8 cm. below the costal margin, and there was marked edema of the lower extremities. The temperature was 99.2° F., and the leukocyte count 10,200 per c.mm.

With absolute rest in bed and digitalis, the pain disappeared in a few hours and the patient improved rapidly. He remained in bed for six weeks and left the hospital at the end of two months. The systolic blood pressure had risen gradually to 172 mm. and the vital capacity to 3100 cc.

Electrocardiograms were taken frequently and always showed auricular fibrillation, at times with varying numbers of ectopic ventricular beats. Four tracings are shown in Fig. 1. At no time were the *T*-wave changes described by Smith[7] and Pardee[4,5] observed.

The patient has been seen frequently since leaving the hospital and on two occasions has been readmitted with cardiac failure of gradual development. In August, 1928, he was feeling very well except for occasional short anginal attacks and slight dyspnea on exertion. He still had auricular fibrillation; the systolic blood pressure was 162 mm. and the vital capacity 2900 cc. There were no new electrocardiographic findings.

Case II.—G. C., a white male, fire captain, aged fifty-eight years, admitted March 1, 1926, complaining of an almost unendurable sense of pressure in the chest. There had been no preceding symptoms of myocardial insufficiency. While walking on the afternoon of the day of admission, he had experienced a short anginal attack. Three hours later, while sitting in a chair, he developed excruciating epigastric and lower sternal pain, followed quickly by a sense of intense, gripping pressure over the entire chest. With this he became dyspneic, nauseated, extremely faint, and very pale. Neither walking nor lying down gave relief. After an hour he was unimproved and was brought to the hospital. On admission, his condition appeared critical. There was marked pallor; the forehead was covered with cold perspiration, and the expression was anxious. Respirations were shallow and moderately rapid. The thorax was somewhat emphysematous in type, and a few crackling râles were heard at the right base posteriorly. The heart extended 11.5 cm. to the left of the midsternal line. The apex impulse was neither visible nor palpable, and the heart sounds were scarcely audible. No murmurs or friction rubs were heard. The peripheral arteries showed moderate sclerosis. The radial pulses were regular, 92 per minute, soft, and easily compressed. Blood pressure was 105 mm. systolic, 75 mm. diastolic. The liver edge was not palpable, and there was no peripheral edema. The temperature was 98.2° F. and the white blood cell count 8400 per c.mm.

In spite of two hypodermic administrations of morphin (gr. $\frac{1}{4}$), pain persisted for over twenty-four hours. On the day after onset, the temperature was 98.8° F., and the leukocytes numbered 7000 per c.mm. The next day the white blood cell count was 14,000 per c.mm., the temperature 99.2° F., and the systolic blood pressure 98 mm. There was no fever after this, but leukocytosis persisted for several days. The patient was kept in bed for six weeks and was discharged without symptoms or signs of myocardial failure at the end of two months. The systolic blood pressure at this time was 118 mm.

Three days after onset, fluoroscopic examination showed only very slight, hardly visible see-saw movement of the heart shadow. Ten days later there was decided improvement in the cardiac excursion, and at a third examination shortly before discharge the contraction was definitely stronger.

Electrocardiograms were taken daily during the period of hospitalization and have been repeated at each return visit. The successive changes observed are shown in Fig. 2.

The patient has been seen frequently since leaving the hospital and, except for slight dyspnea and occasional mild low retrosternal oppression on exertion, has been free of cardiovascular symptoms. At present he is walking three to four miles daily, usually without discomfort. The heart sounds have remained of fair quality, and the systolic blood pressure has fluctuated between 120 mm. and 144 mm.

CASE III.—P. H., a white male, elevator operator, aged sixty-seven years, admitted April 17, 1927, complaining of persistent, severe, retrosternal pain. There had been moderate dyspnea on exertion for two or three years and quite frequent attacks of angina pectoris for one year. On the afternoon of April 16, 1927, while painting a fence, the patient suddenly developed severe, viselike, retrosternal pain radiating to the left shoulder and down the left arm to the elbow. He realized immediately that this was no ordinary anginal attack and later stated, "The pain was a thousand times as severe as any I had had before." Dyspnea, extreme weakness, nausea, vomiting, and profuse perspiration accompanied the onset. The pain was undiminished on admission twenty hours later. Examination showed a dyspneic, restless, apprehensive male. The face was ashen, and the lips were cyanotic. The thorax was moderately emphysematous with numerous crackling râles at either base. Vital capacity was 1600 cc. The heart extended 11 cm. to the left of the midsternal line. The apex impulse was neither seen nor felt, and the heart sounds were of poor quality. No murmurs or friction rubs were heard. The radial arteries were moderately sclerosed, and the pulses were of average quality, 80 per minute. Blood pressure was 130 mm. systolic, 70 mm. diastolic. The temperature was 98° F., and the leukocyte count 14,800 per c.mm.

Two hypodermic administrations of morphin (gr. $\frac{1}{4}$) gave gradual relief, and six hours after admission the patient was quite comfortable. At this time he was showing short paroxysms of auricular fibrillation, an observation made several times in the first four days. On the day after admission severe epigastric and lower retrosternal pain recurred for several hours and was relieved only gradually by morphin. From this time, however, improvement was uninterrupted. Fever and leukocytosis persisted for ten days. The systolic blood pressure dropped slowly to 118 mm. during the first twelve days, but following this there was a gradual rise to 156 mm. at the end of two months. The vital capacity increased coincidentally to 2700 cc. Figure 3 shows the successive electrocardiographic changes observed.

Fluoroscopy of the heart four days after the onset showed moderate diminution of ventricular excursion with extremely weak right auricular contractions and only very slight aortic pulsation. Twelve days later ventricular contraction was somewhat stronger and aortic and right auricular pulsation had increased appreciably. One month later cardiac excursion seemed normal, and subsequent examinations have shown no further changes.

The patient has been seen frequently since discharge, and except for occasional short attacks of angina pectoris and slight dyspnea on exertion, his progress has been uneventful. The systolic blood pressure has dropped gradually to 136 mm., and the vital capacity has varied between 2600 and 2900 cc.

Discussion. The most common cause of cardiac infarction is thrombosis of the coronary arteries due to arteriosclerosis. Extensive thickening of the coronary arteries may occur without producing symptoms or signs of myocardial insufficiency, and the pain of coronary thrombosis may be the first indication of cardiovascular disease. The extent of myocardial infarction in a given case varies according to the size of the vessel occluded. Patients who have involvement of only a very small area may present very mild symptoms; and undoubtedly, as the disease becomes better understood, these cases will be recognized more often.

The striking symptoms and physical signs in cases with relatively extensive infarction usually are sufficient for diagnosis of the condition. In less severe cases, however, information obtained from other observations may be of great diagnostic assistance. The importance of fever, leukocytosis, and low blood pressure is generally recognized. Not uncommonly, as demonstrated in cases reported by Levine[8] and Gager,[9] there is a progressive fall in the systolic reading for several days after the onset. Diminished vital capacity of the lungs gives objective evidence of early circulatory failure; and, since enlargement of the liver and peripheral edema often are absent when the patient is first seen, this information frequently is of value. Marked diminution in cardiac excursion as observed fluoroscopically also may aid in recognizing the disease. The electrocardiogram shows significant features in a majority of cases. The occurrence of sudden changes in cardiac rhythm may aid in diagnosis, and embolism resulting from intracardiac thrombi occasionally is of assistance. The presence of a pericardial friction rub in a condition suggesting cardiac infarction makes the diagnosis certain, but unfortunately this sign is observed in only a small number of patients.

Favorable prognostic signs are progressive rise in blood pressure and vital capacity, improvement in strength of heart sounds, and increase in cardiac pulsation as observed fluoroscopically. Conversely, falling blood pressure after the first few days, decreasing vital capacity, and failure of the cardiac contractions to show improvement on fluoroscopic examination are unfavorable signs. Recovery from cardiac infarction is not attended in every instance by return of blood pressure to normal or high levels; many patients do well for years with a constantly subnormal reading. Repeated fluoroscopic examinations on a large series of patients probably would show likewise that many who recover, but with greatly diminished myocardial reserve, have permanently reduced cardiac pulsation. Symptoms and signs indicative of extension of infarction are to be regarded as of extremely serious import.

The early recognition of coronary thrombosis is of importance because, with proper management, the patient may recover and live for many years. The patients of this series were treated by being kept in bed for at least six weeks. During the first part of this time special nurses were provided, and the patients were not allowed to assist in any movement. Morphin in liberal doses was given for relief of pain, dyspnea, and restlessness. Digitalis was administered only to patients with persistent auricular fibrillation or peripheral congestive failure.

Summary. Three cases of coronary thrombosis with recovery and 6 cases terminating fatally have been studied. The recovered patients have been under observation for from one to about four years after the attack, and all at present are enjoying satisfactory health.

Soon after the occurrence of coronary thrombosis there is commonly a marked reduction below normal of the vital capacity of the lungs. This observation is of diagnostic value because many patients at this time show few peripheral signs of myocardial failure. The conspicuously small cardiac contractions observed fluoroscopically after coronary occlusion are likewise of diagnostic assistance.

Progressive rise in blood pressure and vital capacity and increasing cardiac pulsations observed fluoroscopically are favorable prognostic signs. Conversely, falling blood pressure after the first few days, decreasing vital capacity, and failure of the cardiac contractions to show improvement on fluoroscopic examination are unfavorable signs. Symptoms and signs indicative of extension of infarction are of very serious import.

The early recognition of coronary thrombosis is of importance because, with proper management, the patient may recover and live for years.

NOTE.—I wish to express my appreciation to Dr. Joseph T. Wearn for his kind advice and helpfulness.

REFERENCES.

1. Hamman, L.: The Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp., 1926, **38**, 273.
2. Frothingham, C.: A Case of Coronary Thrombosis, Med. Clin. N. Am., 1927, **10**, 1357.
3. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med., 1920, **26**, 244.
4. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, P. B. Hoeber, Inc., 1928.
5. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms with Special Reference to the Coronary *T* Wave, AM. J. MED. SCI., 1925, **169**, 270
6. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med., 1918, **22**, 8.
7. Smith, F. M.: Electrocardiographic Changes following Occlusion of the Left Coronary Artery, Arch. Int. Med., 1923, **33**, 497.
8. Levine, S. A.: Cases of Coronary Occlusion, with Recovery, Med. Clin. N. Am., 1924, **8**, 1719.
9. Gager, L. T.: Blood-pressure Changes Accompanying Coronary Occlusion, J. Am. Med. Assn., 1925, **84**, 1730.

THE THERAPEUTIC INDICATIONS AND THE DANGERS OF THE INTRAVENOUS ADMINISTRATION OF SODIUM-PHENYL-ETHYL BARBITURATE (SODIUM LUMINAL) AND OTHER BARBITURIC ACID DERIVATIVES.

BY SOMA WEISS, M.D.,

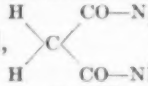
ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.)

SUFFICIENT time has elapsed since the introduction of the hypnotics of the barbituric acid series to allow one to formulate an opinion on their therapeutic value. The following discussion, which

is based on experimental and therapeutic observations, and upon a critical analysis of the literature, attempts to evaluate the problem of the rational application of these substances in a way to be valuable both to clinician and pharmacologist.

The intravenous administration of the barbituric acid derivatives has a distinct therapeutic value. This method of administration is, nevertheless, not without danger if used indiscriminately. A number of pharmacologic and therapeutic actions are identical in all the members of the series. For this reason, the general aspect of the problem will be presented before the discussion of the intravenous administration of the hypnotics.

Definition and Synonyms. The joint chemical, experimental and clinical studies of Fisher and von Mering[1] established in 1903 that while barbituric acid,  , a derivative of urea and malonic acid , is physiologically relatively inactive, the substance obtained by replacement of the two hydrogen atoms by ethyl radicals is a powerful hypnotic in animals and man. This diethylbarbituric acid, commercially called veronal, or barbital, is a more efficient analgesic and hypnotic than chloral, paraldehyde and some other hypnotics. Since the introduction of diethylbarbituric acid into therapeutics, a large number of other barbituric acid derivatives have been prepared by substituting one or both hydrogen atoms with alkyl, cyclic and with a number of other radicals. The possibility of the number of these chemical substances is obviously unlimited. For this reason, under the disguise of various trade names, new therapeutic agents are continuously being introduced by commercial chemical and pharmaceutical houses. Specific claims for the therapeutic superiority of each of these hypnotics are made, although the main action of these substances is highly similar. Physicians are often misled by the different sounding trade names, and often, after discarding one preparation as unsuitable for a certain purpose, take up another with renewed hope. The following are the most widely used barbituric acid derivatives: Diethyl barbituric acid (*veronal* or *barbital*); sodium salt of diethyl-barbituric acid (*sodium veronal;* or *medinal*); iso-amyl-ethyl barbituric acid (*amytal);* iso-allyl-propyl barbituric acid (*allonal*); calcium-ethyl-iso-propyl barbituric acid (*ipral*); n-butyl-ethyl barbituric acid (*neonal*); cyclohexenyl-ethyl barbituric acid (*phanodorn*); phenyl-ethyl barbituric acid (*luminal*) and its sodium salt, *sodium luminal.*

All these names are synonyms for substances which are closely related chemically, in their pharmacologic and therapeutic action.

The Pharmacologic Effects in Animals. If an analgesic or hypnotic dose of any member of the barbituric acid series is administered to dogs, cats, rabbits, or other mammals, the main effects may be summarized as follows: Following the lapse of a period of time, varying mainly according to the channel of administration, the gait of the animal becomes ataxic. Simultaneous with this, excitement may manifest itself occasionally in purposeless struggle, rage, muscular tremor and rigidity. The animal may fall rather suddenly into superficial sleep, shortly to awaken again with excitement. With the onset of deeper sleep, the respirations become slow, occasionally rapid. Periods of Cheyne-Stokes respiration may occur. The cardiac rate is increased. The blood pressure as a rule falls but slightly (10 to 30 mm. of Hg). The peristaltic movements of the gastrointestinal canal stop, as observed under the fluoroscope. The sympathetic centers may also respond partially, provided the sleep is not too deep. The body temperature falls rapidly. The parallelism between the depth of sleep and degree of fall in body temperature is not always strict. In contrast to man, I have never observed rise in the temperature following the administration of barbituric acid derivatives in animals.

Marked fluctuation in the depth of sleep in the same animal, as well as individual variations between different animals are common. A number of factors is responsible for these variations. It was repeatedly observed that animals in dark, quiet rooms go to sleep sooner and after a smaller dose than those tied to a board. Motor or sensory excitement acts antagonistically to the effects of the barbituric acid derivatives. Reversely, a depressed state of the central nervous system acts synergistically. It was shown in a previous investigation[2] and in additional experiments[3] that morphin experimentally produced increased intracranial pressure, and other agents causing respiratory depression act synergistically with the barbituric acid derivatives in producing depression of the respiratory center.

If a fatal dose of the hypnotic is administered, death may result from paralysis of the respiratory center, or may follow a vasomotor collapse with complete loss of heat regulation.

The barbituric acid derivatives may reach the seat of their action through a number of channels of administration. The most frequent methods of administration are the oral, intraperitoneal, intramuscular and intravenous routes.

The onset of sleep may be almost instantaneous following the sudden intravenous injection of about 60 to 70 per cent of the fatal dose. If the injection is slow, however, the excitement may be identical with that observed after oral administration. Eddy[4] observed that the first evidence of action manifested itself in twelve to eighteen minutes after the oral administration of various barbituric acid

derivatives. In my experience, the stage of excitement is more marked with veronal than with amytal and allonal.[5]

Toxicity and Dosage of the Members of the Barbituric Acid Series. The analgesic and hypnotic, as well as the minimal fatal doses of the several derivatives vary considerably when these doses are expressed in actual amounts. It is of the greatest significance, however, that when the analgesic and hypnotic doses are expressed in percentage of the minimal fatal dose, the latitude between the hypnotic and fatal dose is essentially the same. Eddy observed that to induce hypnosis 50 to 60 per cent of the fatal dose of the members of the series he studied had to be administered. I have noted that 60 to 80 per cent of the fatal dose was essential to produce uniform sleep when animals are tied to a board, although 30 to 50 per cent of the fatal dose induced sleep in animals placed in their cages after injection. It was observed that the relative toxicity of veronal, amytal, allonal and luminal is essentially the same when administered intraperitoneally, or intravenously slowly.

The Pharmacologic Effect and the Toxicity of the Barbituric Acid Derivatives in Man. In man, as in animals, the barbituric acid derivatives act as sedatives, analgesics or hypnotics, depending on the amount administered. The toxic effect in man can be studied best on patients who take these drugs accidentally or intentionally. The following description of the pharmacologic effect of the barbituric acid derivatives is based on personal observation of patients, as well as on an analysis of the records of 135 patients admitted to the Boston City Hospital between 1910 and 1928, with acute poisoning due to veronal, luminal and allonal. It is certain, as has also been suggested by Caussade and Tardieu,[6] that the more important toxic reactions of individuals to the various members of the series are essentially the same.

The earliest manifestation of the drug effect is slight confusion with a heavy, dull sensation in the head and ataxia. Difficulty in swallowing, disturbed sense of smell and speech disorders may develop early. Occasionally nausea, vomiting and generalized excitement occur. With the onset of sleep, the rate of respiration usually is reduced and Cheyne-Stokes respiration may develop. If the sleep is deep and of longer duration the respiration is usually rapid and rather superficial. The heart rate is moderately increased and blood pressure slightly lowered (10 to 30 mm. of Hg). The reflexes are unchanged in moderate intoxication. The body temperature may be maintained; more often, however, there is a rise in temperature. A fall in temperature is also observed, but rarely in contrast to the usual occurrence in animals. The kidney function may be disturbed occasionally, as manifested by the presence of albuminuria, oliguria, and less often, anuria.[7] Colored vision, nystagmus, ophthalmoplegia, cardiac pain or a sensation of oppression in the thorax, bradycardia, decubitus, and permanent nerve injury are rarely observed manifestations.

In cases with fatal termination, marked cyanosis, moist skin, rapid, shallow respiration, very low blood pressure and rapid, thready pulse are noted. It is of interest that in two fatal cases of veronal poisoning the deep reflexes were present as late as four and six hours before death. The direct cause of death is usually either pulmonary edema or bronchopneumonia, with final paralysis of the respiratory center. The rise in temperature often develops before there is obtained either clinical or Roentgen ray evidence of bronchopneumonia. The white blood cells are normal until the onset of bronchopneumonia, when they usually increase in number.

Skin eruptions may be absent even upon fatal poisoning, or may appear after administration of small analgesic doses. They are manifestations of idiosyncrasy, rather than of hypersensitivity.

The fatal doses of barbituric acid derivatives in man cannot be estimated with any degree of accuracy from the available accidental or suicidal fatal cases. Aside from the marked individual susceptibility to the action of the drug, the nature of the stomach contents, and the presence or absence of emesis at the early stage of absorption make it difficult to estimate the amount of drug absorbed.

Although occasionally death is reported after such small oral doses as 3 gm. and 6 gm., several patients recovered after 6 or 7 gm. of veronal.[7] Death followed with greater regularity the consumption of over 12 gm. of veronal, although I have seen recovery after the ingestion of 17 gm. It is fair to estimate that for man the fatal dose of veronal usually is from 10 to 15 gm.

The following summary presents a correlation between the amount of veronal taken and the effect. Only those patients are included whose statements were reliable, and they were corroborated with statements of properly informed persons.

EFFECTS OF VARIOUS TOXIC DOSES OF VERONAL IN MAN.

1.5 gm.	No effect.
1.5 gm.	Stuporous, answers questions.
3.0 gm.	Drowsy, disoriented, tendency to sleep.
3.0 gm.	Drowsy, disoriented.
4.2 gm.	Stuporous, ataxic, sleeps twenty-four hours.
4.3 gm.	Drowsy, sleeps twenty-four hours.
6.0 gm.	Deep sleep, reaction serious.
9.0 gm.	Coma, bronchopneumonia, death.
21.0 gm.	Death.

Toxic reactions from luminal are more seldom reported in the literature because it is less frequently used with suicidal intent.[7] It is fair to assume that 4 to 6 gm. of luminal taken by mouth may be fatal frequently. It is also certain that at times much smaller amounts may be fatal.

The estimated fatal dose of 10 to 16 gm. of veronal, and of 4 to 6 gm. of luminal indicates that in an average man of 70 kg. the fatal dose of veronal by mouth is about 143 to 215 mg. per kg., and the estimated fatal dose of luminal is about 57 to 85 mg. per kg. of body

weight. If one compares these amounts with the approximate minimal fatal dose of 300 mg. per kg. of veronal, and 140 mg. per kg. of luminal, in cats and dogs, it seems evident that man is more susceptible to veronal and luminal and probably to other barbituric acid derivatives, than some of the lower mammals.

Intravenous Administration of the Barbituric Acid Derivatives and their Therapeutic Usefulness in Man. Soluble preparations of any barbituric acid derivatives produce almost instantaneous effect in man when administered intravenously. If given intramuscularly the substance enters the blood stream in from five to thirty minutes. The subcutaneous injection of all members of the series causes irritation, and necrosis is apt to result. The symptoms and signs produced by intravenous application are identical with those observed after oral administration. A quantitative comparison of the therapeutic effects of the oral and intravenous administration of identical doses of sodium luminal in patients suffering from epilepsy indicates that the efficiency of the two channels of administration is approximately the same.

The intravenous and intramuscular administrations offer the advantage over oral administration of producing almost instantaneous effects, and as the variable factor of intestinal absorption is eliminated the dosage may be more efficiently regulated to the therapeutic need. In certain conditions, for example, in cocain and novocain poisoning, this instantaneous action may be of life-saving importance. In the majority of conditions in which the barbituric acid derivatives have great beneficial influence, the gastrointestinal channel of administration is not available, because of an agitated state of the central nervous system. Under the following headings are given the more important conditions in which the intravenous application of barbituric acid derivatives has been attempted during recent years.

A. The Problem of Inducement of Surgical Anesthesia. Fredet,[8] in 1925, observed that the combined administration of equal parts of diethylbarbituric acid, allylisopropyl barbituric acid (somnifen) and morphin induce deep sleep and anesthesia. The exact technique of administration is as follows: 10, 15 or 20 mg. of morphin chlorid and 0.66 mg. to 0.75 mg. of scopolamin are administered subcutaneously. Twenty to forty-five minutes later 10 mg. per kg., or an average total of 0.70 gm. of the somnifen is injected intravenously. The patient sleeps within a few minutes after the administration of these barbituric acid derivatives, and the sleep is deep enough to allow the surgical operation to commence with the aid of a few inhalations of chloroform as soon as ten minutes after the injection of the somnifen. Without the aid of chloroform the narcosis and analgesia are insufficient to permit the undertaking of surgical procedures. Bumm[9] found that the intravenous use of "somnifen" is dangerous because of the occasionally observed hypostatic

pneumonia, and marked excitement toward the end of the narcosis. Kidney damage was noted in three patients. He claims that by the attachment of a brompropenyl radical to the barbituric acid the persistence of action of the drug is considerably shortened, and this compound called "pernokton" has a considerable margin between the effective anesthetic and the minimal fatal dose. Raeschke[10] claims that the intravenous administration of a 10 per cent solution of "pernokton," in amounts of 1 cc. per 12.5 kg., or 8 mg. per kg., saves 60 to 80 per cent of the ether necessary for surgical anesthesia; furthermore, it diminishes the pre-operative fear and excitement. "Pernokton" alone cannot be used for the establishment of surgical anesthesia. Plenk,[11] claims that the intravenous administration of "pernokton" in doses of 0.1 gm. per 10 kg. of body weight is not suitable for the production of surgical anesthesia. The respiratory center becomes involved early, and contrary to the statement of Bumm there is but a narrow margin between dose of surgical narcosis and the minimal fatal dose.

In certain instances, however, where the volatile anesthetics are contraindicated or cannot be administered the use of barbituric acid derivatives may be justified.

Although the attempt with "somnifen" and "pernokton" to induce surgical anesthesia proved to be unsatisfactory, recently another attempt was made to use the sodium salt of iso-amyl-ethyl barbituric acid (sodium amytal) for general anesthesia. Zerfas and his associates[12] claim excellent results with sodium amytal as an agent for the induction of general anesthesia in about 300 cases. The dose applied, 20 to 25 mg. per kg., if we consider the possibility that man is more susceptible to the barbituric acid derivatives than animals, is a dose which occasionally may cause severe accidents, for animals may die when given intravenously 50 mg. per kg. of body weight. Sodium amytal does not offer essential advantages over other barbituric acid derivatives and the toxic effects are identical.

Because of these reports, and because experience with animals indicated that complete surgical anesthesia with regularity cannot be induced with the barbituric acid derivatives without considerable risk of life, I have made no attempt to test the surgical anesthetic properties of the barbituric acid derivatives.

In 5 patients, in whom morphin produced excitement, 0.30 gm. of sodium luminal was injected intravenously in a quiet, semidark room to faciliate the inducement of ether anesthesia. The patients became quiet, less interested in their surroundings, and sleepy. The operations were performed under uneventful and uniform ether anesthesia.

The Inducement of Sleep in Certain Psychoses. Kläsi,[13] in 1922, advocated the repeated intravenous use of somnifen to produce sleep, as a therapeutic measure, in certain psychoses. An initial dose of 0.001 gm. of scopolamin and 0.01 gm. of morphin were administered,

followed by the intravenous injection of 0.8 gm. of somnifen. This dose of somnifen then was repeated daily. Demole[14] maintained sleep with intravenous administration of somnifen for twenty-seven days, and Gatti and Cajola[15] for as long as forty days. Furrer[16] administered amounts as high as 0.8 to 1 gm. daily, but Demole[14] concluded that somnifen is dangerous when given in larger doses than 0.5 gm. Müller,[17] in 1925, reviewed the literature and his personal experiences on the intravenous use of somnifen in certain psychoses, and concluded that among the 311 patients receiving somnifen 15 died as a result of this therapy. The immediate cause of death was circulatory failure in 5 instances, pneumonia in 6 cases, in the other 4 patients other etiologic factors were present, but somnifen was a contributing cause of death. Individual variations in the reactions of patients to this barbituric acid derivative were very marked. Evidence of weakened circulation, rise of temperature, and other signs of severe intoxication occurred frequently. Müller concludes that although the therapeutic principle of induced sleep in certain phases of manic depression is beneficial, the intravenous administration of somnifen is dangerous. It is of interest that, notwithstanding this discouraging experience, Müller,[18] in 1927, reports his results with the closely related soluble preparation of dialyl barbituric acid, commercially called dial. On the morning of the first day 0.4 gm. of dial with 0.5 mg. of scopolamin or 2 mg. of a papaverin preparation called "Paron Ciba" was given. This dose was followed by the intravenous administration of from 0.2 to 0.4 gm. in the evening, depending upon the state of the patient. The average daily amount of dial was 0.58 gm. in men, and 0.54 gm. in women. The patient usually begins to sleep only after the second day. Although fever and pneumonia developed in the treated patients, Müller believes that dial is less dangerous than somnifen. From the reports available it is evident, however, that the depth and uniformity of sleep were more marked with somnifen than with dial. This suggests that the difference in toxic reaction has to be attributed rather to the difference in the minimal fatal dose, than to the specific characteristics of the two hypnotics. The therapeutic effect of dial according to Müller was beneficial in mania. It was of doubtful value in schizophrenia.

Eclampsia. The value of sedatives in eclampsia is well established. It is rational, therefore, that the action of barbituric acid derivatives has been investigated in this condition.

Süss[19] claims a beneficial influence in eclampsia due to the repeated subcutaneous administration of 0.4 gm. of sodium luminal (2 cc. of a 20 per cent solution) at six-hour intervals up to 1.6 gm. daily. This amount is combined with venesection. Eberhard[20] also found marked improvement after the intravenous administration of 0.4 gm. of sodium luminal three times daily, combined with from 15 to 20 mg. of morphin or from 50 to 100 mg. of papaverin. In

addition, oxygen was freely administered and 500 cc. of blood were removed through venesection. Eberhard believes that this method of treatment should replace the present widespread use of the Strogonoff[21] treatment. In Eberhard's 57 cases the mortality rate of the mother was 5.97 per cent and that of the child 23.5 per cent.

Epilepsy. The beneficial effect of the oral administration of phenol barbital (luminal) in epilepsy was established in 1912. Wyler[22] observed that the intravenous injection of from 0.2 to 0.4 gm. of somnifen checked the status epilepticus in three instances. In epileptic patients Patterson, Damon and Levi[23] used routinely by intravenous injection 0.12 gm. of sodium luminal, which at two-day intervals was increased by 0.06 gm. up to the maximal single dose of 0.3 gm. Untoward effects were not observed in over one hundred injections. Aside from the oral administration, the intravenous or intramuscular administration of the barbituric acid derivatives is indicated in severe status epilepticus, which condition because of persistent seizures, is of imminent danger to the patient's life, and at the same time the gastrointestinal channel is not available for administration.

Luminal sodium has been administered intravenously in 12 patients who were in status epilepticus, with evidence of circulatory collapse and pulmonary edema. The status lasted from two to fifteen hours before the first intravenous injection was given. Gradually increasing doses were given at intervals of one-half hour in order to establish the minimal effective dose. The amounts which controlled the convulsions varied from 0.4 to 1 gm. In one case a larger dose was required. In general, the amounts necessary to control convulsions were proportional to the severity of the motor irritation of the central nervous system. Eleven of the patients recovered, one died after the convulsions were controlled. This patient's condition was critical before the administration of the luminal, and it is therefore impossible to determine whether or not the luminal was a contributing factor.

Toxic Reactions due to Certain Local Anesthetics. The observations of Hofvendahl[24] and Tatum, Atkinson and Collins and others[25] clearly show that veronal and luminal may prevent otherwise fatal experimental cocain poisoning in animals, including monkeys. Following these observations, Leshure[26] reported that while morphin alone, or combined with scopolamin, did not prevent the occasional toxic reactions due to local anesthetics, from 0.4 to 0.8 gm. of sodium veronal administered by mouth routinely before operative procedures with a local anesthetic was efficient to prevent toxic reactions. Williams[27] used 0.3 gm. of barbital two hours and one hour before the beginning of operations with local anesthetics. He also noted beneficial results. Martin[28] observed that the frequency and severity of toxic reactions due to novocain were considerably reduced in patients receiving 0.60 gm. of barbital the

night before, and one hour before surgical operation. Guttmann[29] also has reported that the routine hypodermic administration of from 0.18 to 0.3 gm. of barbital reduces the frequency of toxic reactions following the use of novocain.

That the proper intravenous administration of the barbituric acid derivatives is useful, not only as a preventive agent when administered before the use of local anesthetics, but also when injected after an alarming toxic reaction develops following local anesthesia, is shown by the observations herewith recorded.

Case Reports. Case I.—T. C., a white boy, aged sixteen years, entered the hospital with a crushed right hand, which was caught in a machine. Except for this local condition, the physical examination revealed no abnormal findings. He was much excited. The arm was shaved and scrubbed with soap and water. Novocain infiltration with a 2 per cent solution of novocain at the elbow was started. After 50 cc. of novocain were injected the patient developed instantaneous violent convulsions. The convulsions recurred at about one- to two-minute intervals. The convulsions could not be controlled by immediate administration of ether. These seizures lasted for over thirty minutes. The patient became increasingly cyanotic, and signs of pulmonary edema developed. The pulse rose to 140 and was thready. The rectal temperature rose to 102.5° F. The patient's condition was considered critical. Administration of oxygen failed to benefit the patient. The administration of ether was stopped. The intensity of convulsions increased.

Thirty-five minutes after the onset of the convulsions, the intravenous injection of sodium luminal (10 per cent solution) was started. In three minutes, 450 mg. were injected and convulsions stopped instantly. Cyanosis gradually disappeared and the cardiac action became stronger. The pulse dropped to 110 per minute within thirty minutes. The pulmonary edema cleared up. Two hours later the patient was conscious. The surgical operation with ether was performed uneventfully on the following day and the patient was discharged three days later.

From the observations it is very suggestive that the intravenously administered sodium luminal saved the life of the patient.

Tetanus. During the past three years we have administered intravenously a 10 per cent solution of sodium luminal in 5 cases of tetanus. All the patients were suffering from pain and showed generalized spasm of the musculature with recurrent convulsions. The presence of opisthotonus prevented the performance of spinal puncture necessary for therapy in 3 of the patients. The administration of sodium luminal was indicated both for the comfort and for the recovery of the patient. The oral administration was not practical. Because experience on animals and on other patients indicated that the maximal hypnotic effect of the drug manifested itself within a few minutes, the method of administration finally adopted was to inject the drug continuously at a rate of 20 mg. per minute. When the onset of sleep and muscular relaxation were noted the injection was stopped. It was observed that the amount necessary to produce muscular relaxation varied from 0.8 to 1.2 gm.

Following the injection of such an amount of sodium luminal,

complete relaxation developed although the sleep was superficial and the patient responded to pinching of the skin. The beneficial effect of a single dose of luminal lasted for from two to four hours, depending upon the severity of the increased muscular tone and the convulsions. The second dose necessary to overcome the muscular spasm was smaller. The respiration usually became slow about twelve minutes following the injection, and it then returned to normal. The systolic blood pressure dropped an average of 20 mm. of Hg, the diastolic 15 mm. of Hg. The temperature was unchanged, or showed a further rise after luminal. Three of the five patients died, the other two recovered.

It is thought that these 3 patients were in such desperate condition that death was inevitable, and that luminal did not influence the outcome.

Case II.—R. Y., a white woman, aged forty years, confessed chronic morphin addiction. A few days before admission to the hospital she took frequent doses of morphin subcutaneously without sterilizing the needle. Two days before her entry her neck became stiff and later gradually her entire body became "stiff."

When seen she was unable to speak because of the trismus. The expression of the face was typically that of *risus sardonicus*. There was a complete fixation of the jaw. The neck was stiff. The respiration was rapid, about 30 per minute. The heart rate was slightly increased. The systolic blood pressure varied between 90 and 106 mg. of Hg, the diastolic between 65 and 80 mm. of Hg. The extremities were rather rigid. The deep reflexes were hyperactive. Occasionally tonic convulsions were present.

The intraspinal administration of tetanus antitoxin was not possible because of the general condition of the patient.

At 7.23 P.M. slow intravenous injection of a 10 per cent solution of sodium luminal was commenced. In the following ten minutes 1.3 gm. were injected.

At 7.45 P.M. the patient's jaw and the entire body relaxed; the patient was able to speak and complained of sleepiness and the injection was stopped.

At 7.52 P.M. the patient went to sleep and her body became relaxed. She was not in coma, however, and on pinching the skin responded with defensive motions of the extremities. The respiration was 17 per minute with periods of apnea and the face was flushed. The cardiac rate was 100. The blood pressure was 90 systolic and 60 diastolic. The rectal temperature was 99.4° F.

At 8.35–36 P.M. a 10 per cent carbon dioxide and 90 per cent oxygen mixture was administered. Respiration became deep and regular, indicating that the respiratory center was not severely depressed. Blood pressure was 80 systolic and 60 diastolic. Cardiac rate, 78. Rectal temperature, 99° F. Reflexes diminished but present.

At 9.20 P.M., during administration of an alcohol rub, the patient awakened.

At 9.38 P.M. the patient resisted the subcutaneous injection of physiological salt solution.

At 10 P.M. sleep was very superficial but the patient was nevertheless completely relaxed. Blood pressure was 80 systolic and 60 diastolic; heart rate was 78.

At 11.45 P.M. the patient awoke, and muscular spasm returned. Sodium luminal, 0.5 gm., was administered again intravenously. The patient

relaxed and slept again. Following this second dose the patient slept with the exception of short periods until 9 A.M.

At 9 A.M. the patient was awake. She was able to speak. The neck was slightly resistant but not stiff. Physical examination revealed suggestive signs of bronchopneumonia. Blood pressure was 104 systolic and 80 diastolic; respiration, 44; heart rate, 130; temperature, 101° F.

At 10 A.M. muscular spasm was back. After slow intravenous administration of 0.500 gm. of sodium luminal the patient was completely relaxed and slept. For several minutes Cheyne-Stokes respiration occurred.

At 11 A.M. the patient was awake again. 0.500 gm. of sodium luminal was administered. Patient relaxed and slept superficially.

At 3 P.M. the patient relaxed. Blood pressure was 90 systolic and 60 diastolic; respiration, 46; heart rate, 135; temperature, 103° F. Patient perspired freely. Definite clinical evidence of consolidation of the lower lobe of the left lung was elicited.

At 8 P.M. the sleep was still superficial. Patient was becoming comatose. She was cyanotic, perspired freely, and respiration was regular, rapid, but not labored. There developed clinical evidence of pulmonary edema and circulatory collapse. Temperature was 103.6° F.

At 9 P.M. the patient died.

During her stay in the hospital the patient received 47,000 units of tetanus antitoxin.

In this patient 2.8 gm. of sodium luminal was required to overcome muscular spasm and to induce sleep for twenty-five hours.

Cerebral Hemorrhage with Convulsion. The prompt relief of convulsions occurring in patients with cerebral injuries due to trauma or to intracranial hemorrhage is of great therapeutic significance in checking the extent of permanent intracranial damage. Sodium luminal was administered in intravenous doses of from 0.5 to 1.5 gm. in 3 patients with convulsions due to traumatic injury of the skull, and to 4 patients who, as a result of arterial hypertension, developed cerebral hemorrhage. The convulsions in all 7 patients were promptly relieved. Two of the hypertensive and one of the patients with traumatic injury died, as a result of pulmonary edema and bronchopneumonia, following an increasing coma lasting for from eighteen to twenty-six hours.

Persistent Hiccough. Six-tenths to 1 gm. of sodium luminal failed to stop persistent hiccough, although the patients became drowsy and sleepy. Two of the patients developed persistent hiccough of two and three days' duration after surgical operation on the prostate, the other three during a course of bronchopneumonia. The fact that the hiccough occurred simultaneously with each respiration indicates that this reflex is closely related to the respiratory reflex, which cannot be essentially influenced with safe doses of sodium luminal. This does not rule out that hiccough of less severity may not be influenced by proper doses of intravenous luminal.

Discussion. From the evidence presented it is clear that the pharmacologic and toxicologic effects of the various members of the barbituric acid derivatives are, with slight variations, the same in animal and in man. One of the most striking differences is the effect on the heat regulation. The different members of the series produce essentially identical effects in man, the existing differences

concern the intensity of excitement preceding the sleep and the persistence of action. Although the effective analgesic and the fatal dose vary considerably with the different members, there is a fairly uniform relationship between the analgesic, hypnotic, and fatal doses of different members of the series of the barbituric acid derivatives. In cats the analgesic effect was absent up to and including the administration of 30 per cent of the average fatal dose of a number of the members of the barbituric acid series. To produce stupor amounting to anesthesia at least 50 per cent of the average fatal dose was required. It is estimated that the fatal dose of sodium luminal in man is 3 to 4 gm.; the minimal amount producing sleep and moderate anesthesia varies from 0.7 to 1.5 gm. This indicates that 23 to 37 per cent of the fatal dose in man produces sleep and moderate relaxation and partial anesthesia. Man is therefore more sensitive to the toxic effect of the barbituric acid derivatives than animals, and in addition, a slightly lower percentage of the fatal dose is effective to produce analgesia and hypnosis. If Keeser's[30] observations are correct that the brain tissue has a special affinity for barbituric acid derivatives, then the relatively large bulk of the human brain may be one of the factors in producing this increased susceptibility.

Among the conditions determining the marked individual variations in the analgesic and fatal doses, the intensity of the afferent impulses to the central nervous system and excitability of the central synapses play a most fundamental rôle. Pain, sympathetic excitement, worry and fever act antagonistically to the effect of barbituric acid derivatives; while central depression is synergistic and, therefore, makes the patients susceptible to the depressant effect of the barbituric acid. As the clinical determination of the state of the central nervous system is not possible with any degree of accuracy, the effective use of the barbituric acid derivatives without individual consideration of the patient is not possible without incurring considerable danger.

Just as the dosage to produce a certain effect depends on the stage of the central nervous system, so also the persistence of action varies. Continuous sleep of over twenty-four hours' duration was observed after a single intravenous administration of 0.5 gm. to an epileptic patient, in whom the agitated state of the central nervous system was only temporary. On the other hand, the effect of 1.5 gm. of sodium luminal may last but about three hours in a patient with tetanus, in whom the abnormal impulses are persistently active.

Because of the marked variation in the effective dose, as well as in the persistence of action, the amount administered should be regulated for each patient. The routine dosage should be guided by the behavior of susceptible individuals. As the effect of the intravenous administration manifests itself almost instantaneously, and as the maximum effect, at least with luminal, is reached within from five to fifteen minutes after the injection, it seems advisable to

inject a 10 per cent solution of sodium luminal at a rate of about 50 mg. per minute, until the desired effect is obtained. The initial dose, however, should not exceed 1.5 gm. in an average adult.

With every therapeutic dose of barbituric acid derivatives sufficiently large to produce deep and persistent sleep, there is a potential danger of fever, circulatory collapse, secondary hypostatic congestion of the lungs, bronchopneumonia, and occasionally lobar pneumonia. The danger of these toxic manifestations increases considerably if an attempt is made to maintain hypnosis for several days, as has been attempted by investigators in certain types of psychosis. Bronchopneumonia or lobar pneumonia may develop during the period of recovery from the drug effect, and it may run a usual course after the patient has recovered from the direct effect of the hypnotic.

A comparison of the therapeutic efficiency of the barbituric acid derivatives with that of morphin, ether, chloroform, and nitrous oxid in various pathologic conditions suggests a different mechanism of action. The barbituric acid derivatives often influence functions of the central nervous system on which ether and morphin have no or only slight effect. The fact that the hypnotic effect of the members of the barbituric acid series is maintained or even increased after decerebration;[30] that disturbances in certain medullary functions may occur early and before the onset of sleep; and finally that these hypnotics are preëminently effective in abolishing the effect of cocain and novocain, substances which have specific action on the medulla and midbrain; all indicate that the hypnotics of the barbituric acid series have a specific affinity, influencing the functions of certain centers of the midbrain and medulla.

Observations both in animals and in man clearly show that severe motor disturbances may develop as a result of administration of the barbituric acid derivatives before there is an appreciable dulling of the sensory system. This also indicates that the gaseous anesthetics cannot be replaced by barbituric acid derivates, and that the indications for their use are different. Ether, chloroform and other volatile anesthetics are more efficient analgesics than are the barbituric acid derivatives. On the other hand, the latter may be more effective than the former in certain motor excitement such as convulsions, increased muscular tone and emesis.

Summary. 1. The evidence presented herein suggests that man is more susceptible to the barbituric acid derivatives than animals, and that in man a relatively smaller percentage of the fatal dose produces analgesia and narcosis.

2. Marked individual variations exist in the response of patients to identical doses. The state of the central nervous system is one of the important factors which determines the variations in the intensity of effect, and in the persistence of action. Sensory and motor excitement act antagonistically, while depression acts synergistically with the barbituric acid derivatives.

3. Sodium luminal injected intravenously in doses of from 0.4 to 1.2 gm. at a rate of 50 mg. per minute in a 10 per cent solution stops convulsions, produces muscular relaxation, and induces sleep with considerable regularity. The narcosis even after such large doses may be superficial and the analgesic effect may be only partial. The effect of a single dose may last as long as twelve hours.

4. In certain patients with severe status epilepticus, eclampsia, grave toxic reactions from local anesthetics, convulsions due to cerebral hemorrhage or with tetanus the intravenous administration of sodium luminal and other barbituric acid derivatives is of distinct therapeutic value.

5. The routine use of the intravenous hypnotic dose of the barbituric acid derivatives for surgical anesthesia, or for the inducement of sleep of days' duration in certain psychoses is dangerous.

6. The mechanism of the action of the barbituric acid derivatives is different from that of ether, chloroform, and nitrous oxid. These anesthetics usually cannot be replaced by the barbituric acid derivatives. The hypnotics of the barbituric acid series have marked inhibitory influence on certain medullary and midbrain centers.

7. The dose administered to a patient should be determined by the individual behavior of the subject during the slow intravenous administration of the hypnotic. In the pathologic conditions discussed the intravenous administration of large sedative or hypnotic doses should be administered only if the condition of the patient is critical, and other measures which are just as efficient and more safe are not available. It should be remembered that a hypnotic dose of any barbituric acid derivative entails potential danger for the patient.

REFERENCES.

1. Fisher, E., and von Mering, J.: Ueber eine neue Klasse von Schlafmittel, Ther. d. Gegenw., 1903, **5**, 97.

2. Norris, V. H., and Weiss, Soma: The Pharmacological and Therapeutic Properties of Alpha-lobelin. A Comparison of its Action on the Respiratory Center with that of Other Respiratory Stimulants, J. Pharm. Exp. Ther., 1927, **31**, 43.

3. Weiss, Soma: Unpublished experiments.

4. Eddy, N. B.: Studies on Hypnotics of the Barbituric Acid Series, J. Pharm. Exp. Ther., 1928, **33**, 43.

5. Weiss, Soma: Anesthesia Induced by the Barbituric Acid Derivatives, with Special Reference to Associated Blood Sugar Changes, Proc. Soc. Exp. Biol. and Med., 1926, **23**, 363.

6. Caussade, G., and Tardieu, A.: Intoxication aigue par le Véronal et les autres dérivés de la malonylurée, Bull. et mém. Soc. méd. d. hôp. de Paris, 1925, **49**, 295.

7. Seifert, O.: Die Nebenwirkungen der modernen Arzneimittel, 2 Aufl. Curt. Kabitzsch., Leipzig, 1923.

8. Fredet, P.: L'anesthesie génèrale chirurgicale au moyen de l'allyl-isopropyl-malonylurée, Paris méd., 1925, **2**, 479.

9. Bumm, R.: Intravenöse Narkose mit Barbitursäurederivaten, Klin. Wchnschr., 1927, **6**, 725.

10. Raeschke: Verbesserung der Äthernarkose mit Pernokton, Klin. Wchnschr., 1928, **7**, 1014.

11. Plenk, A.: Erfahrungen mit Pernoctonschlaf bei chirurgischen Operationen, Wien. klin. Wchnschr., 1928, **2**, 1557.

12. Zerfas, L. G., McCallum, J. T. C., Shoule, H. A., Swanson, E. E., Scott, J. P., and Clowes, G. H. A.: Induction of Anesthesia in Man by Intravenous Injection of Sodium Iso-amyl-ethyl-barbiturate, Proc. Soc. Exp. Biol. and Med., 1929, **26**, 399.

13. Kläsi, J.: Ueber die therapeutische Anwendung der "Dauernarkose" mittels Somnifens bei Schizophrenen, Ztschr. f. d. ges. Neurol., 1922, **74**, 557.
14. Demole, V.: La cure sédative en psychiatrie, Jouve and Cie, Paris, 1922.
15. Gatti, G., and Cajola, R.: Ricerche cliniche e spermentali sull' azione ipnotica e tossica di un nuovo ureide dell' acido malonico: il "Somnifen," G. Frederici, Pesaro, 1921.
16. Furrer, J.: Unsere Erfahrungen mit der Somnifen Narkose bei Psychosen, Schweiz. med. Wchnschr., 1924, **5**, 275.
17. Müller, M.: Die Dauernarkose mit Somnifen in der Psychiatrie, Ztschr. f. d. ges. Neurol. Psych., 1925, **96**, 653.
18. Müller, M.: Die Dauernarkose mit flüssigem Dial bei Psychosen, Speriell bei manisch-depressivem Irresein, Ztschr. f. d. ges. Neurol. u. Psych., 1927, **107**, 522.
19. Süss: Unsere Erfahrungen mit der Rissmann'schen Eklampsie Behandlungen, Münch. med. Wchnschr., 1924, **71**, 980.
20. Eberhard, H. F.: Weitere Erfahrungen mit unserer Eklampsiebehandlung, Ztschr. f. Geburt. u. Gyn., 1927, **92**, 204.
21. Strogonoff, W.: Die prophylaktische Behandlung der Eklampsie und die dabei erzielten Erfolge, Monatschr. f. Geburt. u. Gyn., 1909, **29**, 567.
22. Wyler, J.: Weitere Erfahrungen mit Somnifen in der Psychiatrie, Ztschr. f. d. ges. Neurol. u. Psychiat., 1924, **94**, 20.
23. Patterson, H. A., Damon, L. G. A., and Levi, P.: A Comparative Study of Various Methods of the Administration of Luminal in Epilepsy, J. Nerv. and Ment. Dis., 1926, **63**, 446.
24. Hofvendahl, A.: Die Bekaempfung der Cocain-vergiftung im Tierversuch, Bioch. Ztschr., 1921, **117**, 55.
25. Tatum, A. L., Atkinson, A. J., and Collins, K. H.: Acute Cocain Poisoning, its Prophylaxis and Treatment in Laboratory Animals, J. Pharmacol. and Exp. Ther., 1926, **26**, 325.
26. Leshure, J.: Barbital as a Preventive of Cocain Toxicosis, J. Am. Med. Assn., 1927, **88**, 168.
27. Williams, C. B.: Barbital to Prevent Toxicosis from Local Anesthesia, Laryngoscope, 1927, **37**, 921.
28. Martin, E. G.: Local Anesthesia Agents, J. Am. Med. Assn., 1928, **91**, 555.
29. Guttmann, M. R.: Acute Cocain Intoxication, J. Am. Med. Assn., 1928, **90**, 753.
30. Keeser, E.: Zur Pharmacologie der Hypnotika, Deutsch. med. Wchnschr., 1928, **54**, 650.

AN INTRATRACHEAL METHOD FOR PROLONGED ARTIFICIAL RESPIRATION.

By Leopold Brahdy, M.D.,
ASSISTANT SURGEON, MT. SINAI HOSPITAL,
AND
M. Bernard Brahdy, M.D.,
ASSISTANT ATTENDING PHYSICIAN, WILLARD PARKER HOSPITAL, NEW YORK.

(From the Laboratory of the Department of Pharmacology. College of Physicians and Surgeons, Columbia University, New York.)

When artificial respiration is required for a few hours only, as in resuscitation after drowning the Schaeffer method is simple and efficient.[1] For prolonged periods the necessity of relays of attendants working constantly makes the application of the Schaeffer method difficult. Manual methods of artificial respiration have

been used without success in the treatment of the respiratory paralyses of poliomyelitis and diphtheria. It is possible that the exhaustion of the patient by the manipulation contributed to the fatal outcome.

Pharyngeal methods of artificial respiration, such as the pulmotor, have many disadvantages. The control of the intrathoracic pressure is difficult; vomitus and saliva may be forced into the lungs; air may be forced into the stomach.

Meltzer, in 1910, suggested, for clinical use, continuous intratracheal insufflation or as he called it "continuous respiration without respiratory movement."[2] In his method a catheter is passed into the trachea and the lungs are distended by air under constant pressure. The lungs are allowed to collapse by a complete interruption of the air current two to four times a minute. The method is based on the theory that the composition of the alveolar air can be changed by diffusion from the trachea through the distended bronchioles. The continuous air current accomplishes an important secondary result: the uninterrupted flow of air out of the larynx prevents saliva and vomitus from entering the lungs.

We began our present work with the idea that the Meltzer method was satisfactory. Our first failures were ascribed to too high or too low air pressure. More careful experiments indicated that the cause of failure was inherent in the method. If prolonged artificial respiration was to be successful a new method had to be devised.

Experimental Respiratory Paralysis. Methods of artificial respiration were tested on cats whose respiratory center had been destroyed by pithing or paralyzed by drugs. Paralysis by drugs permits the study of complications after the animal has recovered from the toxic action of the drug. At first we used curare to stop respiration but found it unsatisfactory. Divided doses of amytal gave better results. The amytal required varied widely ranging from 120 to 255 mg. per kg. As soon as respiratory movements ceased, artificial respiration was instituted. About every two hours the artificial respiration was stopped for one or two minutes to ascertain if the animal would breathe naturally. Respiratory paralysis lasted from two and a half to twelve hours.

Experiments with the Meltzer Method. A technical difficulty of the Meltzer method is the necessity of placing the catheter opening 1 cm. or less above the bifurcation of the trachea. Attempts were made to pass the catheter until the bifurcation was felt and then to withdraw it 1 cm. In cats, the catheter slips into a bronchus so easily that it is impossible to feel when the bifurcation is reached. It was necessary to determine the ratio:

$$\frac{\text{Length (in centimeters) of the cat}}{\text{Distance (in centimeters) from incisor teeth to bifurcation.}}$$

In 22 out of 29 cats the ratio was fairly constant, 2.3. In 75 per cent of cats therefore, $\frac{\text{length of cat}}{2.3}$ = the distance that the tracheal catheter must be inserted in order to lie 1 cm. or less above the bifurcation. In the remaining 25 per cent the incorrect position of the catheter caused failures. In the 22 experiments in which the catheter was properly placed the Meltzer method was sometimes successful. However, frequent failures occurred. Several animals died of circulatory collapse apparently due to the continuous high intrathoracic pressure. Two cats died of distention of the stomach with air, a complication described by Meltzer. In none did the method maintain life for more than five and a quarter hours. Cats with the respiration paralyzed by drugs either resumed natural breathing before the end of five and a quarter hours or they died. Pithed cats died before the end of four and a half hours.

These difficulties of the Meltzer method suggest why it has never come into common use. The following new technique has been devised which overcomes the difficulties and retains the advantages of the Meltzer method.

The New Method. Our method makes use of an intratracheal catheter. It differs from the Meltzer method in that the lungs are expanded every four seconds by air under pressure, then allowed to collapse and remain collapsed for three seconds. The alveolar air is changed, as in natural respiration, by movement of the lungs. During the stage of collapse the flow of air through the catheter continues but under very low pressure, not sufficient to expand the lungs. This produces an uninterrupted escape of air from the larynx.

The Catheter. A soft rubber catheter is introduced into the trachea through the larynx. With cats this is done by direct laryngoscopy using a urethral endoscope. In contrast with the Meltzer method it is not essential that the catheter lie at the bifurcation. It may lie anywhere in the lower half of the trachea. The catheter has two openings to insure patency under all conditions. For cats of 2 to 4 kilograms No. 14 Fr. is satisfactory. For larger animals a No. 16 Fr. is preferable. The relation between the size of the catheter and the size of the larynx is unimportant. The catheter is connected with the special respiration pump.

The Intermittent Expanding Pressure. Every four seconds a current of air under pressure is passed through the catheter for one second. This expands the lungs. The pressure is adjusted until the chest expansion is the same or slightly less than in normal breathing. The pressure does not develop suddenly but rises gradually, thus avoiding undue strain on the lung tissue. The pressure is measured by a mercury manometer and it is the same for animals of a size if the same size catheter is used. With a larger catheter a lower pressure produces the same effect.

The Constant Pressure. During the interval between expansions, the inflow of air is not stopped entirely. A constant stream of air passes through the catheter into the trachea and out of the larynx. The pressure of this stream is low enough to allow complete collapse of the lungs. The purpose of this constant stream of air is to prevent any saliva or vomitus from passing into the lungs.

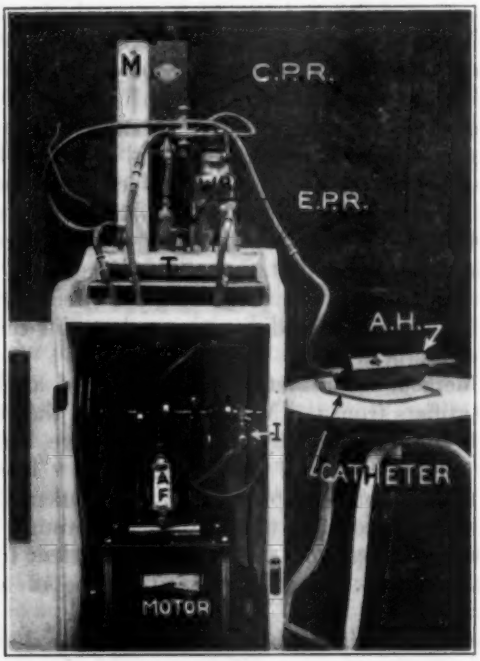


FIG. 1.—Apparatus for prolonged artificial respiration. The air passes from the motor-driven pump through the air filter *AF* to the tank *T*. From the tank the air may pass into the water bottle in two ways. Either through the direct connection controlled by the constant pressure valve *CPR*—or through the interrupter *I* which opens at intervals. The pressure of the latter air current is controlled by the expanding pressure regulator *EPR*. From the water bottle *WB* the air passes through the air heater into the catheter. A side-arm connects the manometer *M*.

The Apparatus. The apparatus[1] consists of several parts. There is a motor driven three-piston pump connected with a small tank (Figs. 1 and 2). Between the pump and the tank is an air filter (*AF*) which removes any coarse dust particles or oil. There are two connections from the tank to the tracheal catheter. The intermittent expanding air current passes through the interrupter (*I*). This is arranged to permit air to pass through every four seconds.

[1] The cost of the apparatus was defrayed by a grant from the Jeremiah Milbank Fund for the Study of Infantile Paralysis. Manufactured by C. M. Sorensen Co., Long Island City, N. Y.

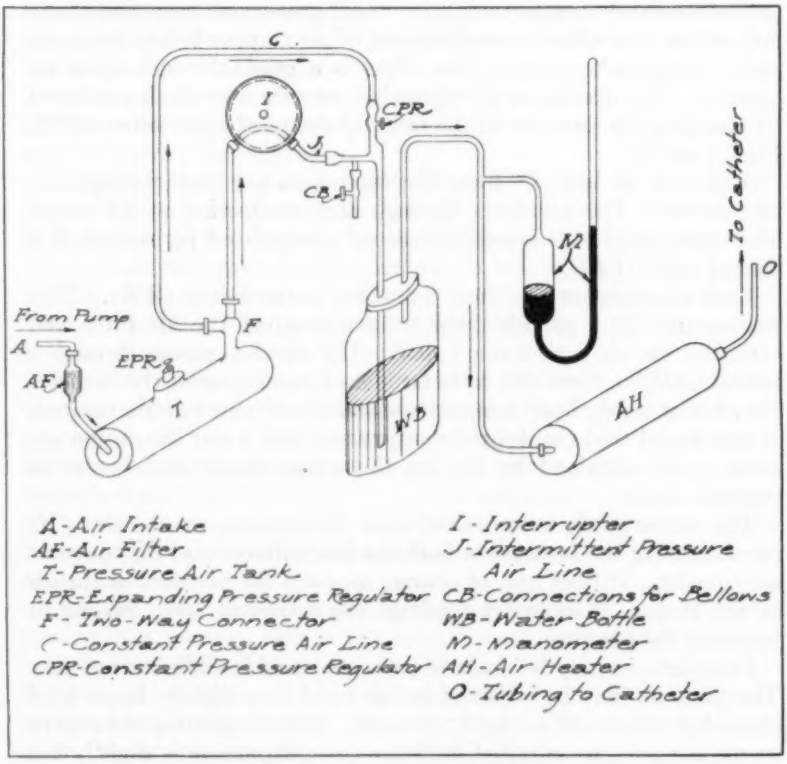


FIG. 2.—Diagrammatic representation of the apparatus.

FIG. 3.—Detailed diagram of the interrupter.

The interrupter consists of a solid disklike core (*R*, Fig. 3) with a V-shaped passage through it. This disk revolves inside a stationary housing. The housing has two connections (air inlet and air outlet, Fig. 3) so fixed that once during each revolution of the disk they

are connected by the air passage. Small grooves on each side of the hole in the disk allow a small current of air to pass before the complete coincidence occurs. The effect is a gradually increasing air current. The maximum to which this pressure may rise is regulated by changing the pressure in the tank by means of a pin valve (*EPR*, Figs. 1 and 2).

A second air line (*C*) from the tank does not pass through the interrupter. The air flows through this connection at all times. The pressure of this constant current is regulated by means of a thread valve (*CPR*).

Both air currents pass into the water in the bottle (*WB*). This washes out dust particles which have escaped the air filter and saturates the air with water vapor. The air then passes through a heater (*AH*) and into the catheter. As it comes out of the catheter the air is at nearly body temperature and 50 per cent water saturated. It was found that the desired temperature and water saturation are more easily obtained by having the water bottle and heater in separate units.

The water bottle is connected with the mercury manometer (*M*) for measuring the pressure of both the intermittent and the constant air current. It does not, of course, measure the pressure of the air in the lungs. Manometer readings are a control when raising or lowering the pressure.

Comparisons may be made of pressures used in different animals. The pressure may be adjusted before hand to a slightly lower level than that which will probably be used. After beginning the experiment, the pressure is raised until the chest expansion is slightly less than in normal breathing.

The New Method in Decerebrated Pithed Cats. The new method of artificial respiration was uniformly successful in cats with the respiratory center destroyed by pithing. Although we did not continue any experiments more than twelve hours, the indications were that the animals could have been kept alive much longer. When it was decided to terminate an experiment, the pump was stopped and the animal allowed to die of asphyxia. Postmortem examination showed injection of the trachea. The lungs were normal. The following protocol illustrates this group of experiments:

EXPERIMENT NO. 44, APRIL 21, 1928. LENGTH OF CAT, 48 CM.

Time.	Heart.	Temperature.	Remarks.
8.40	105	..	Catheter passed 19.5 cm. and animal pithed. Artificial respiration by the new method.
8.55	120	39.2	
10.0	210	37.8	
11.05	170	37.6	
12.05	152	38.4	
2.0	168	38.2	
4.10	174		
6.0	160	38.6	
7.55	168	38.2	Artificial respiration stopped. Cat allowed to die of asphyxia.

Comment on Experiment No. 44. The respiratory center was destroyed by pithing and decerebration. The new method of artificial respiration was used for eleven and a quarter hours. The condition of the cat was satisfactory throughout the experiment. The cat was allowed to die of asphyxia; the catheter was left *in situ* and the thorax was opened.

The catheter was connected with the artificial respiration apparatus. At intervals of four seconds the intermittent air pressure caused good expansion of the lungs followed by collapse. The constant air pressure caused no expansion whatsoever, evidenced by the fact that there was no further collapse when both air currents were turned off. The trachea was slightly injected. The lungs and other organs were apparently normal.

The New Method; Respiration Paralyzed by Drugs. The catheter was inserted into the trachea and then the respiratory center was paralyzed. When there was no longer any sign of natural respiration the catheter was connected to the respiration apparatus. The animals were kept alive until natural respiration returned. Then the catheter was removed. In order to ascertain whether there were any late complications the animals were observed from three to seven days.

One cat died of pneumonia three days after it had artificial respiration. Several cats in the animal room not subjected to any experimental procedure died at this time.

With this exception the animals took their food well and showed no ill effects after recovery from the drug. Three to seven days after the experiment they were killed. A complete postmortem examination with special reference to the trachea and the lungs showed no pathologic changes. The following protocol illustrates this group and shows the technic used:

EXPERIMENT NO. 46, APRIL 25, 1928. LENGTH OF CAT, 50 CM. WEIGHT, 2.5 KG.

Time.	Heart.	Temperature.	Remarks.
8.40	..	..	Amytal 120 mg. per kg. intraperitoneally.
8.55	..	..	Catheter passed 19.5 cm.
9.0	126	36.2	Stopped breathing. Artificial respiration started.
10.15	129	36.5	
11.30	140	37.2	
1.15	145	37.6	
2.30	160	38.0	
3.50	144	37.4	
5.0	136	37.2	Respiration 20. Returned to cage.
April 27	..	..	Eating.
May 1	..	..	Animal killed. Autopsy.

Comment on Experiment No. 46: Respiration was paralyzed with 120 mg. of amytal per kilogram of body weight. The new method of artificial respiration was successfully used until natural breathing returned—eight hours.

We tested for the return of function of the respiratory center several times by discontinuing the artificial respiration one to two minutes. After recovery from the drug, the animal appeared normal. To hasten recovery from the narcosis, caffeine was injected the day after the experiment.

After recovery from the drug, the animal appeared normal. It was observed for six days and then killed. The trachea was moist and normal. The lungs and other organs were normal.

Criterion of the Return of Respiratory Function. It is important to note that the animals did not breathe naturally as long as artificial respiration was adequate. After artificial respiration was stopped the apnea lasted, at times, as long as two minutes. We tested for the return of respiratory function by disconnecting the catheter for two minutes. The animal either breathed or the heart rate rose rapidly. If the heart rate rose, the catheter was again connected and artificial respiration resumed. The short period of asphyxia was apparently harmless. A better test for the return of function is to stimulate the respiratory center by distending the lungs a few times with air or oxygen containing 5 to 10 per cent carbon dioxid. If the respiratory center is functioning, the animal will breathe almost immediately.

The Intrabronchial Pressure. The thorax was opened in pithed decerebrated cats kept alive with artificial respiration. A cannula was inserted into one of the main bronchi and connected with a water manometer. The intrabronchial pressure of the expanding air current was 4 to 8 cm. of water. The constant air current which caused no movement of the lungs, produced an intrabronchial pressure of ½ to 1 cm. of water. When both air currents were disconnected there was no further collapse of the lungs. Although we know that 6 cm. of water is the pressure required for adequate expansion of the lungs, this measurement cannot be made before the end of the experiment. The only criterion as to how much pressure to use in a particular case is to compare the expansion with a natural respiratory movement, and raise the pressure high enough to approximate the natural expansion. This can be done very easily.

Advantages of the New Method. 1. After proper adjustment no manipulation of the patient is necessary; the artificial respiration procedes automatically.

2. Saliva and vomitus are not forced into the lungs, but are prevented from gravitating into the lungs.

3. The intratracheal catheter may be placed anywhere in the lower half of the trachea.

4. Excessive pulmonary pressure is guarded against. Sudden increase of the pulmonary pressure does not occur.

5. Circulatory failure is not likely to occur because the high intrapulmonary pressure is maintained for only a short time.

6. Distention of the stomach with air does not occur.

7. Feedings may be given by gavage.

Clinical Application. The method was used in two cases of poliomyelitis with complete respiratory paralysis. The patients were cyanosed, pulseless and showed no signs of any muscle movement when artificial respiration was begun. Normal color and pulse returned and were maintained in one patient for nine hours and in the second patient for twelve and a half hours; at the end of that time the heart stopped. It seems reasonable to assume that the respiratory paralysis in some cases of poliomyelitis may be transient as are some of the skeletal paralyses. If such is the case, artificial respiration should be maintained until the recovery of the center or death from circulatory failure. The clinical application will be reported in detail in another paper.

Conclusion. A new method of artificial respiration is described which has been used successfully in animals. Clinically it has been used in two cases and should be tried more extensively.

NOTE.—We are indebted to Prof. C. C. Lieb for the privilege of working in his laboratory and for his helpful suggestions.

REFERENCES.

1. Drinker, C. K.: Acute Asyphyxia as a Medical Problem. J. Am. Med. Assn., 1928, **90**, 1263.
2. Meltzer, S. J., and Auer, J.: Continuous Respiration without Respiratory Movements, J. Exper. Med., 1909, **11**, 622.
3. Meltzer, S. J.: Die Methode der intratrachealen Respiration, Berl. klin. Wchnschr., 1910, **47**, 566.

REVIEWS.

PRACTICAL MATERIA MEDICA. By CLAYTON S. SMITH, PH.D., M.D., and HELEN L. WIKOFF, PH.D., Department of Physiological Chemistry and Toxicology, College of Medicine, Ohio State University. Pp. 284. Philadelphia: Lea & Febiger, 1929. Price, $3.25.

THIS book is intended primarily for the medical student. It contains concise summaries of the properties and preparations of important drugs, inorganic and organic, as well as sections dealing with toxicology and with prescription writing and incompatibilities. Structural formulæ are given with welcome frequency. The suggested laboratory exercises in connection with the various drugs are concerned chiefly with pharmaceutical preparation and assaying, but directions for chemical experiments with many drugs are given in the section on toxicology. The book contains the material for a comprehensive course in materia medica and toxicology, and is recommended to teachers of those subjects. C. S.

DIABETIC SURGERY. By LELAND S. MCKITTRICK, M.D., F.A.C.S., Visiting Surgeon, Palmer Memorial Hospital; Assistant Surgeon, New England Deaconess Hospital; Surgeon to Outpatients, Massachusetts General Hospital; and HOWARD F. ROOT, M.D., Assistant Physician, New England Deaconess Hospital; Associate in Medicine, Peter Bent Brigham Hospital and Palmer Memorial Hospital; with a Foreword by DANIEL F. JONES, M.D., and ELLIOTT P. JOSLIN, M.D. Pp. 269; 79 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1928. Price, $4.25.

NINE years ago, a well-known authority on diabetes in writing on the subject dismissed the surgical complications of the disease rather briefly, explaining that "they occupied much space in older textbooks but are becoming less numerous as diabetes is earlier diagnosed and better treated." The experience of the intervening years has, however, been quite different. While the mortality rate from diabetes throughout the country has actually increased, in the last few years, as recently pointed out by Dr. F. L. Hoffman, fewer and fewer of the deaths have been due to coma, thanks to insulin; on the

other hand, surgical conditions have accounted for a steadily increasing percentage of the fatalities. Prior to 1922, 9.8 per cent of Joslin's fatal cases were due to surgical conditions, while in the period 1925 to 1927 the surgical-death percentage was 71. This book is, therefore, a most timely one, and coming, as it does, from associates of Dr. Joslin, it represents the fruits of a large experience. Surgeons will, of course, read it; but the Reviewer wishes particularly to recommend it to internists and practitioners, for, "In most cases diabetic patients with gangrene die a surgical, not a medical death. This is usually due to neglect on the part of the patient, procrastination on the part of the family physician and, too often, delay on the part of the surgeon or internist." R. K.

THE MOBILIZATION OF ANKYLOSED JOINTS BY ARTHROPLASTY. By W. RUSSELL MACAUSLAND and ANDREW R. MACAUSLAND. Pp. 252; 154 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $4.00.

A MONOGRAPH presenting its subject in a concise manner and from the viewpoint of the surgeon. Written by one of the foremost exponents of the use of arthroplasty in the restoration of function with stability to ankylosed joints.

The treatise is thorough; the recommendations conservative; much of the material has appeared in various publications by the senior author. G. W.

CLINICAL PHYSIOLOGY (A SYMPTOM ANALYSIS) IN RELATION TO MODERN DIAGNOSIS AND TREATMENT. A TEXT FOR PRACTITIONERS AND SENIOR STUDENTS OF MEDICINE. By ROBERT JOHN STEWART MCDOWALL D.Sc., M.B., F.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London. With an Introduction by W. D. HALLIBURTON, LL.D., F.R.C.P., F.R.S., Emeritus Professor of Physiology, King's College, University of London. Pp. 383; 4 illustrations. New York: D. Appleton & Co., 1927.

IN his preface the author defines the reason why he wrote this book.

"Some years ago it was my fortune to take an active part in the teaching of clinical medicine and, during that period, it was possible to study in some detail how far the average medical student was able to adapt his knowledge of the science of Physiology to his practical requirements. It was fully realized that the study of Physiology in its more scientific aspects was in every way desirable, but it was clearly seen that for the adequate appreciation of the signs and

symptoms of disease more was necessary than is normally taught by the physiologist or clinician. It is, for example, extremely difficult—indeed almost impossible from a study of ordinary textbook Physiology—for him to see why a cardinal symptom of cardiac disease should be breathlessness.

"This volume is an attempt to present some of the facts of physiology and their applications in general medicine in a form which fits in conveniently with pathologic and clinical teaching."

The author discusses briefly such phenomena as:

The venous pulse and the heart sounds, blood pressure, the effect of hemorrhage and allied conditions on the circulation, cyanosis and breathlessness, vitamins, growth, swallowing and digestion, formation and excretion of bile, etc. The Reviewer finds it necessary to criticize the extreme brevity with which some of the subjects discussed have been treated. However, there is a great deal of well written useful information, which should help the student and the practitioner better to understand the functional disturbances brought about by disease processes. B. L.

OLD AGE. THE MAJOR INVOLUTION. THE PHYSIOLOGY AND PATHOLOGY OF THE AGING PROCESS. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories, University of Michigan, Ann Arbor. Pp. 199; 29 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $3.00.

AN enlargement of the author's Carpenter Lecture before the New York Academy of Medicine, the thesis is developed that the involution processes of old age are essentially physiologic in nature. Thus Metchnikoff's orthobiosis is opposed on the one hand, and the various attempts at rejuvenation, on the other. The demonstration by Carrel's tissue cultures that even mammalian cells are potentially immortal is cursorily dismissed as an irrelevant pathologic process. To some people, however, there already exists support for believing that many of the phenomena of old age can with more reason be considered pathologic and therefore perhaps removable. Impressed, perhaps overimpressed, with the idea that the whole life process is "chiefly, or solely, for the attainment of one end that the species shall not perish from the earth," the author logically contemplates all postfertile ages with what philosophical equanimity he can muster, as part of the gradual process of decay. Analogies with plant life are obvious, but for practical human purposes at least, the inestimable achievements attained by individuals in the so-called involution period would better have received more attention and emphasis. Many will be surprised to learn that "un-

doubtedly the fourth decade brings the best results" in progeny and that "ideal ages for marriage are twenty-eight to thirty years in the male, and twenty-six to twenty-eight years in the female," even though the offspring alone is here being considered. The distinguished author is making a stoical and apparently successful effort to apply the last words of his book—Goethe's quotation: "Keine Kunst ist's alt zu werden, es ist Kunst es zu ertragen;" whether such an attitude will tend to retard our scientific knowledge of senility and the eventual happiness of the aged is, however, a different question. E. K.

THE TONSILS AND ADENOIDS AND THEIR DISEASES. By IRWIN MOORE, M.B., C.M. (EDIN.), Late Honorary Surgeon to the London Throat Hospital for Diseases of the Throat, Nose and Ear, Great Portland Street, and also to the Hospital for Diseases of the Throat, Golden Square, London, W. Pp. 395; 107 illustrations and complete bibliography. St. Louis: The C. V. Mosby Company, 1928. Price, $6.50.

THIS is an eminently practical book on the diseases of the tonsils and adenoids. The anatomy, pathology and surgery, including the various methods of controlling hemorrhage, with many illustrations is clearly described. A complete chapter on tonsils, as a source of focal infection in systematic diseases with extensive references is noteworthy.

In it you will find the opinion and case reports of the best-known otolaryngologists in the world, with numerous reports of fatalities following tonsil and adenoid operation. The book is well written, and diseases of the tonsils and adenoids including the lingual tonsils are clearly described. This should be an excellent book for medical students, general practitioners and a reference for specialists.

D. H.

PHARMACOTHERAPEUTICS. By SOLOMON SOLIS-COHEN and THOMAS STOTESBURY GITHENS. Pp. 1869. New York: D. Appleton & Co., 1928. Cloth. Price, $15.00.

THIS is a treatise on drug therapeutics, but it is unique in several respects. It is written primarily for the clinician, and, therefore, contains details of preparations, mode of administration and of results to be expected, that are not found in books dealing with pharmacology. The discussions of pharmacological and toxicological features are more authoritative and up to date than is the

case with treatises on therapeutics. Of particular value are the sympathetic discussions of many agents which, because their employment rests wholly upon empirical observations, are given scant consideration in current works upon pharmacology. The history of each drug is sketched with unusual thoroughness. Newer remedies, such as chaulmoogra and ephedrin, are given adequate consideration, as are serums, vaccines, antigens, etc. This book contains information that is available in no other single work that is known to the Reviewer, and is highly recommended to experimenters as well as clinicians. C. S.

ANTENATAL CARE. By W. E. T. HAULTAIN, O.B.E., M.C., B.A., M.B. (CAMB.), F.R.S.C.E., Senior Assistant Obstetric Physician to the Antenatal Department, Edinburgh Royal Maternity and Simpson Memorial Hospital; and E. CHARLES FAHMY, M.B. (EDIN.), F.R.S.C.E., Assistant Obstetric Physician, Antenatal Department, Edinburgh Royal Maternity and Simpson Memorial Hospital. With a Foreword by PROF. R. W. JOHNSTONE, C.B., M.A., M.D., F.R.S.C.E., Professor of Midwifery and Diseases of Women, University of Edinburgh. Pp. 108; 2 illustrations; 2 charts. New York: William Wood & Co., 1929. Price, $2.25.

THIS small but meaty book is a description of the methods of antenatal practice of the Edinburgh school. The measures recommended are modern and coincide closely with the generally accepted teaching in the United States. The single criticism might be that no metric equivalents are given for the various pelvic and cephalic measurements. The therapy of various antenatal disorders, toxemias, syphilis and gonorrhea are detailed. This is an excellent manual for the prenatal clinic worker. P. W.

PROGRESSIVE RELAXATION. By EDMUND JACOBSON, A.M., PH.D., M.D., of the Physiological Laboratory, the University of Chicago. Pp. 429; 69 illustrations and figures. Chicago: The University of Chicago Press, 1929. Price, $5.00.

THIS serious study of rest has extended over a period of twenty years and a new method is given for the treatment of hypertension—a term preferred to neurasthenia unless actual exhaustion is present.

Through his muscle sense, the subject is taught to recognize tension by movements of the body that will cause contraction in any given part and with this fundamental knowledge, he proceeds to undo his own hypertension.

The treatments vary in duration, frequency and over the period of time employed.

Many conditions are cited as being greatly benefited and among others, hypochondria. Right here the author runs counter to accepted authority. The less a hypochondriac meddles with his body, the better. What he needs is to be guided away from himself —plenty of wholesome work and a hobby.

While the procedure appears to have merit, there is an unpleasant amount of fault-finding with other methods. An extensive bibliography is appended. N. Y.

THE NOSE, THROAT AND EAR AND THEIR DISEASES. In Original Contributions by American and European Authors. Edited by CHEVALIER JACKSON, M.D., Sc.D., LL.D., F.A.C.S., Chevalier de la Legion d' Honneur; Chevalier del 'Ordre de Leopold, Professor of Bronchoscopy and Esophagoscopy in the University of Pennsylvania, in the Jefferson Medical College and in the Graduate School of Medicine of the University of Pennsylvania; Lecturer on Bronchoscopy and Esophagoscopy in the Women's Medical College of Pennsylvania and in Temple University, Philadelphia; and GEORGE MORRISON COATES, A.B., M.D., F.A.C.S., Professor of Otology, University of Pennsylvania Graduate School of Medicine; assisted by CHEVALIER L. JACKSON, A.B., M.D., Assistant in Bronchoscopy and Esophagoscopy, University of Pennsylvania and the Graduate School of Medicine, University of Pennsylvania. Pp. 1177; 657 illustrations and 27 inserts in colors. Philadelphia and London: W. B. Saunders Company, 1929. Price, $13.00.

SUCH a volume on the diseases of the nose, throat and ear with so many distinguished and internationally known authorities has never been published before. European and American authorities under the supervision of the authors have written this complete book.

The anatomy, pathology, diseases and treatment, medical and surgical of the nose and sinuses with a complete chapter on sinuses in children and their diagnosis and complication with clear-cut illustrations is the last word.

Anatomy and diseases of the ear, including the surgery and complications of the mastoid operation with many beautiful illustrations cannot be improved upon at this time.

The chapter on the larynx which takes up four hundred pages, a book in itself, is a classic in its field and a most reliable guide for the laryngologist. The endoscopic views and drawings of Jackson are inimitable.

This book belongs to the highest type of medical writing, editing and publishing in this country. It is a credit not only to its authors but to its editors as well, and no otolaryngologist can afford to be without it. D. H.

BOOKS RECEIVED.

NEW BOOKS.

*A History of the Medical Department of the United States Army.** By COL. P. M. ASHBURN. Pp. 448. Boston and New York: Houghton, Mifflin Company, 1929.

*Stephen Hales, D.D., F.R.S.** By A. E. CLARK-KENNEDY. Pp. 256; 14 illustrations. New York: The Macmillan Company, 1929.

*The Custom of Couvade.** By WARREN R. DAWSON, F.R.S.E. Pp. 118; 1 illustration. Manchester, England: The Manchester University Press, 1929. Price, 7/6.

*Clinical Aspects of Venous Pressure.** By J. A. E. EYSTER, B.Sc., M.D. Pp. 135; 7 illustrations. New York: The Macmillan Company, 1929. Price, $2.50.

*The History of Hemostasis.** By SAMUEL CLARK HARVEY, M.D. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

*An Introduction to the Study of Physic.** By WILLIAM HEBERDEN. Pp. 159; 6 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $2.00.

The Physiology of Love. By GEORGE M. KATSAINOS, PH.D., M.D. Pp. 326. Boston: Privately printed, 1929. Price, $4.00.

*Gonorrhea and Kindred Affections in the Male and Female.** By GEORGE ROBERTSON LIVERMORE, M.D., F.A.C.S., and EDWARD ARMIN SCHUMANN, M.D., F.A.C.S. Pp. 257; 66 illustrations. New York: D. Appleton & Co., 1929. Price, $5.00.

Collected Papers of the Mayo Clinic and the Mayo Foundation, 1928. Volume XX. Pp. 1197; 288 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $13.00.

Eighty-one papers are printed entire, 43 abridged, 72 abstracted and of 233 references only are given.

Medical Department of the U. S. Army in the World War. Volume X: Neuropsychiatry. Pp. 543; 3 illustrations. Washington: U. S. Government Printing Office, 1929.

Medical Department of the U. S. Army in the World War. Volume III: Finance and Supply. Pp. 935; 50 illustrations. Washington: U. S. Government Printing Office, 1929.

Medical Department of the U. S. Army in the World War. Volume XII: Pathology of the Acute Respiratory Diseases and of Gas Gangrene following War Wounds. Pp. 583; 312 illustrations. Washington: U. S. Government Printing Office, 1929.

*Osteomyelitis and Compound Fractures and Other Infected Wounds.** By H. WINNETT ORR, M.D., F.A.C.S. Pp. 208; 54 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $5.00.

Progressive Medicine, Volume II, June, 1929. Pp. 389; illustrated. Philadelphia: Lea & Febiger, 1929.

* Reviews of titles followed by an asterisk will appear in a later number.

Diabetes Latente. By Dr. Felix Puchulu. Pp. 213. Buenos Aires: Talleres Graficos Ferrari Hnos, 1929.

*The Conquest of Cancer.** By Daniel Thomas Quigley, M.D., F.A.C.S. Pp. 539; 334 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $6.00.

*The Modern Dance of Death.** By Peyton Rous, M.D. Pp. 51. Cambridge, England: Cambridge University Press, 1929.

*Pathologico-anatomical and Clinical Investigations of Fibro-anemonatosis Cystica.** By Carl Semb. Pp. 484; 37 illustrations. Oslo: National-brukkeriet, 1928.

Surgical Clinics of North America, New York Number, Volume IX, No. 3, June, 1929. Pp. 299; 125 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*Tumores Primitivos de la Pleura.** By Jose W. Tobias. Pp. 479; 60 illustrations. Buenos Aires: El Ateneo, 1928.

*Principles and Practice of Electrocardiography** By Carl J. Wiggers, M.D. Pp. 226; 61 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $7.50.

*The Life of Hermann M. Biggs, M.D., B.Sc., LL.D.** By C.-E. A. Winslow, Dr.P.H. Pp. 432; 35 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $5.00.

NEW EDITIONS.

Manual of Diseases of the Nose, Throat and Ear. By E. B. Gleason, M.D., LL.D. Sixth edition. Pp. 617; 268 illustrations. Philadelphia: W. B. Saunders Company, 1929.

A careful revision with special attention given to the criticisms of teachers of otolaryngology.

Clinical Laboratory Methods. By Russell Landram Haden, M.A., M.D. Third edition. Pp. 317; 73 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $5.00.

A few new methods such as the Kahn precipitation test and the determination of indican in the blood have been added.

Diseases of the Thyroid Gland. By Arthur E. Hertzler, M.D. Second edition. Pp. 286; 159 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $7.50.

*A Manual of Proctology.** By T. Chittenden Hill, Ph.B., M.D., F.A.C.S. Third edition. Pp. 272; 86 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $3.50.

Practical Chiropody. By E. G. V. Runting. Third edition. Pp. 200; 21 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $3.00.

A practical booklet containing much sound advice about small but very often troublesome matters.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Blood Platelets in Splenic Anemia, with Special Reference to Treatment by Splenectomy.—EVANS (*Lancet*, 1929, i, 277) presents an interesting paper on the blood platelets in anemia which is primarily of importance because of the correlation of platelet count with indication for operation. He notes, first, that the hemorrhagic tendency in splenic anemia may be due either to a mechanical factor, probably related to venous stasis associated with splenic and portal thrombophlebitis, or with a thrombopenia. He states that thrombosis of splenic veins and portal veins is of frequent occurrence and that thrombosis both in the portal system and the peripheral system may occur as a postoperative complication, occasioning at times a gross and persistent increase in the platelets after removal of the spleen. The patients that show a thrombotic tendency have normal or elevated platelet counts before splenectomy. These patients are operated upon with considerable risk because of the possibility of thrombosis, which may be fatal. It is possible, on the other hand, to recommend splenectomy with the greatest amount of confidence in those cases in which there is a thrombopenia. The article then gives a word of warning which should be of importance to medical men and to the patient: operate on the thrombocytopenic group, but keep away from operative procedures in the thrombocythemic group.

A Study of the Nature of the Urea Concentration Test and its Value as a Test of Renal Function.—There have been innumerable types of tests advocated for the determination of the functional efficiency of the kidney. Some of these, and often these more complicated tests give the most information, have been discarded because of technical difficulties which prevent their general use in the study of any considerable number of patients suffering from nephritis. Others have not stood up, when extensively used, to even a fair degree of accuracy. The two functional kidney tests most widely used in this country at the present

time include the well-known phenolsulphonephthalein test of Rowntree and Geraghty, which is entirely an estimation of the kidney function at the time the examination is done, and some one or another modification of the dilution-concentration ability of the kidney. The urea concentration test appears to be quite generally employed in England since its introduction by McLean and De Wesselow in 1920. WINTROBE (*J. Lab. and Clin. Med.*, 1929, **14**, 848) writes that this particular functional test is of theoretic value because it is simple and it represents the test of a function normal to the kidney. He shows in his studies that it is relatively accurate. Substantiation of this latter statement is found in the study of forty-nine healthy students whose kidney function was contrasted, after the usual laboratory examinations which excluded gross nephritis, by two methods, phthalein elimination and urea concentration. They both indicated that the kidney was healthy but the urea test seems to be a very imperfect quantitative indicator of the function of the kidney because of the variations in concentration of urea which occur possibly as a result of, but depending upon, alterations in the amount of urine excreted. In the series of fifty-six patients who were believed to have nephritis on clinical findings, the urea-concentration test proved definitely superior to the phthalein where there was passive congestion from cardiac failure.

Variability of the Tubercle Bacillus.—The wave of enthusiasm that has swept over France and some other European countries, following the announcement of Calmette that he has been able to vaccinate babies against tuberculosis by feeding them attenuated living preparations of the tubercle bacillus, has not been received in this country with more than a certain healthy skepticism. Indeed, many objections have actually been advanced on theoretic grounds, despite the ever-increasing thousands of children in Europe who have been treated without harm up to the present at least. What the future will bring out is another question. PETROFF (*New England J. Med.*, 1929, **200**, 1148) at a recent meeting of the Massachusetts Tuberculosis League explained why he considered the method unsafe and told how the Bacillus Calmette-Guerin (B. C. G.) had been elaborated. Briefly, the development of this apparently harmless strain of tubercle bacilli depends upon the principle of microbic dissociation, "the process of variation in the offspring from the mother colony. Upon cultivation, this variation can be demonstrated first by cultural characteristics . . . upon subsequent cultivation there will be many variants from the mother colony. The two, or, perhaps, three, variants may differ from each other not only in colony structure, but also in tinctorial characteristics, virulence and other biologic characteristics." In Petroff's experimental work he was able to develop from a common mother colony two distinct dissociated strains, R colony and S colony, the former avirulent, the latter virulent for guinea pigs. This research explains B. C. G.; but, and a very big but, the R strains may be mutated into the S cells by certain procedures, such as cultivation in media containing 5 to 10 per cent homologous antiserum and the R strains are apparently not entirely free from some organism of S strain, no matter how carefully cultivated. These last two observations most assuredly present experimental evidence indicating possible dangers of feeding B. C. G. to children.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Complications and Mortality of Appendicitis.—WARREN (*Lancet*, 1929, ii, 16) writes that appendicitis appears to be developing a more severe character or is more common. The disease shows a considerable variation in its severity, depending on time and place. The mortality in the author's experience varies from 3 to 10 per cent. Expectant treatment may give good results in certain hands, but as a general measure its advantages are not proved, and its wide adoption might lead to further disasters. The mortality is greatest in children who are certainly not cases for expectant treatment, owing to the rapid and insidious way in which complications, such as peritonitis, develop in young subjects and their liability to acidosis from starvation. Early diagnosis and immediate operation are the counsels of perfection, but failure to diagnose early is by no means always the fault of the practitioner, for in children and old people the diagnosis may be quite difficult and many people regard a stomach ache too lightly. The main causes of death are peritonitis and mechanical obstruction. The latter can be very largely prevented by suitable technique at operation, and a careful watch should be kept in this important complication.

Surgery of the Esophagus.—SAINT (*Arch. Surg.*, 1929, **19**, 53) states that the problems which have rendered surgical procedures in this sphere so difficult, and which still remain to be overcome, have been discussed. They lie in the anatomic structure and relationship of the esophagus and in the risk of fatal infection of the pleura and the cellular tissue of the neck and mediastinum. The numerous operations devised and performed for the extirpation of esophageal carcinoma have resulted in an appalling mortality. It is pointed out that such tumors are highly malignant, that they metastasize readily and that by the time they give rise to symptoms they usually have spread beyond the limits of surgical removal. The various methods used for the plastic formation of a new esophagus in cases of benign cicatricial stricture believed to be impermeable are described. There is a mortality of 20 per cent in the cases reported in the literature. This reason makes plastic operations undesirable procedures, to be avoided by early and adequate dilatation and by impressing on the patient the necessity for further dilatation at stated intervals. It would seem too that plastic operations have been undertaken unjustifiably, in many cases, the inability to pass the smallest sound being taken as the indication of impermeability. In nearly all such cases, however, a swallowed silk thread can worm its way through the stricture and then be used as a guide for sounds.

The Use and Abuse of Iodized Oil in the Diagnosis of Lesions of the Spinal Cord.—Craig (*Surg., Gynec. and Obst.*, 1929, **49**, 17) says that iodized oil injected into the subarachnoid space is an invaluable adjunct in the armamentarium of the neurologist and the neurologic surgeon in diagnosing compression of the spinal cord, but it has its use and abuse. This diagnostic procedure should always be employed in conjunction with a complete examination, and the results obtained should never occupy more than relative importance in the establishment of a diagnosis. The irritative action on the meninges contraindicates its use in frank inflammatory lesions. By the use of iodized oil, the presence of tumor of the spinal cord can be detected earlier in certain cases, and the fact that there is a response to jugular pressure does not preclude its use. The outstanding use of lipoidol is for the confirmation of a suspected tumor of the spinal cord, and its greatest abuse is its employment in cases in which a complete examination would have established a diagnosis.

Hypernephroma.—Judd and Hand (*J. Urol.*, 1929, **22**, 10) claim that carcinomas of the renal cortex are extremely malignant and are often well advanced before they produce symptoms. Alveolar carcinomas, in which but little attempt at cellular differentiation is made, are the most highly malignant of the various types of renal carcinoma, whereas adenocarcinomas are less malignant as judged from their clinical course. It is necessary that all of these malignant tumors should be submitted to gradation on the basis of cellular differentiation before it will be possible to arrive at more exact knowledge of the effect of treatment and the prognosis in the individual case. Not all of these deaths were due to the malignant condition. Many of these patients have lived for several years and then died from other causes. Some were known to have metastasis at the time they were operated upon and from the evidence at hand it would seem that the condition was arrested for a time. Therefore, even in these cases nephrectomy could seem to offer a reasonable degree of palliation. From the fact that 106 of their patients lived from three to twenty-two years, the authors believe that they are justified in the opinion that surgery will cure a definite proportion of them.

Pyelography and Cholecystography.—Eisendrath and Areus (*Surg., Gynec. and Obst.*, 1929, **49**, 1) say that the older criteria, as emphasized by Cole, in 1917, which were employed to differentiate the shadows of biliary and renal calculi are of little value at the present time. One can exclude from consideration the coral-like or branching renal calculus. The anatomic juxtaposition of the gall bladder and kidney in normal persons makes it possible to confuse shadows of biliary with those of renal calculi. The radiographic opacity of any calculus is not only dependent upon the atomic weight of the constituents, but to the structure and thickness of the calculus. Soft calculi are much less opaque than hard calculi. The form and opacity of biliary and renal calculi have many points of resemblance, so that these two criteria alone cannot be considered pathognomonic. The range of mobility of biliary calculi, is as a rule, greater than that of renal or ureteral calculi. If, however, the latter have formed in a dilated renal pelvis or ureter,

or both, a wide range of migration is possible. Cholecystography or pyelography or these two methods combined are very valuable additions to our diagnostic resources in the differentiation of biliary and renal calculi. Multiple exposure should be made by rotating the patients, because in some positions the suspected calculus may appear in the gall bladder or the kidney, while in others its true position is at once evident.

Impression Resulting from Three Thousand Transfusions of Unmodified Blood.—BLAIN (*Ann. Surg.*, 1929, **89**, 917) claims that favorable results obtained from 3000 transfusions have stimulated enthusiasm regarding transfusions and have made the clinic determined to extend the treatment not only to frank anemias, but to complicated surgical cases and bad surgical risks. Even moderate anemia before operation means prolonged and stormy convalescence after operation. Severe hemorrhage produces a deficiency of valuable blood constituents other than corpuscles and iron. Chronic secondary anemia without apparent cause, or persisting after the cause is removed, constitutes the basis of many cases of poor "health" and "chronic invalidism." A simple method whereby unmodified blood can be rapidly transferred from donor to recipient should be employed, and exposure of the blood to the air should be avoided. Universal donors may be used safely. A transfusion properly given presents practically no contraindications and produces essentially no reactions.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Rectal Administration of Liver in Pernicious Anemia.—In view of the occasional almost total inability of certain patients with pernicious anemia to eat adequate amounts of liver in any form whatsoever, and at times even to take orally any of the liver extracts, HANS PULFER (*Deutsch med. Wchnschr.*, 1929, **55**, 99) tried the rectal administration of liver in 2 cases with results quite as satisfactory as those usually obtained with its oral administration. The liver, finely ground, thinned with milk and then passed through an exceedingly fine sieve, was prepared for rectal administration by the addition of 15 drops of tincture of opium. This thin mixture was then injected slowly into the rectum which had previously been prepared with a low cleansing enema. A

daily dose of 150 grams of liver was thus administered. In order to increase the effectiveness of this mode of administrating liver hepatopson, a liver extract was frequently added to the prepared liver. No difficulty was observed in having these enemas retained and their absorption seemed to be rapid and complete.

The Surgical Treatment of Angina Pectoris Based on Researches upon Man.—As a result of his prolonged investigations concerning the mechanism of angina pectoris, along with consideration of the investigations of others, DANIELOPOLU (*Weiner klin. Wchnschr.*, 1929, **42**, 67) supports his previous concluslons that one of the most important influences responsible for the attacks is that of a pressor reflex. He further points out the very high mortality of the Jonnesco operation and the serious and lasting after effects of many modifications of this operation in which either the inferior cervical ganglion, the stellate ganglion or both are resected. The author finds it possible to avoid these dangers and at the same time to obtain equally effective relief of the attacks by a much simpler procedure. He advocates the removal of the superior cervical ganglion on the left side, leaving intact the inferior ganglion and the stellate ganglion. The connecting branches, however, which lead out of the inferior cervical ganglion as well as those which pass to the sixth, seventh and eighth cervical and first dorsal segments are sectioned. In addition, the vertical branches of the vagus in the neck are cut and the vertical nerve is also severed. This procedure not only diminishes the pain or prevents its occurrence but is also associated with an appreciable and lasting diminution in the blood pressure. It has been performed in approximately 25 patients with the foregoing results and so far has proved entirely free from danger.

Endonasal Administration of Insulin.—Seeking a method of administering insulin other than by hypodermic injection, WASSERMEYER and SCHAFER (*Klin. Wchnschr.*, 1929, **8**, 210) experimented with its application intranasally. They employed a powdered insulin which was mixed with pure borax. In tests on normal subjects they found a noticeable reduction in blood sugar two hours after the administration of 17 units and a somewhat less marked reduction with smaller doses. Similiar results were obtained in a small group of well-controlled diabetic patients as illustrated by the fact that the fasting blood sugar was reduced from 183 to 74 mg. within two and a half hours after a dose of 13 units. Equally satisfactory results were obtained in others. Further investigations on less well-controlled ambulant patients confirm the fact that insulin is well absorbed following intranasal administration. The one question not yet settled by their investigation is that of whether or not the dose by this mode of administration is susceptible of sufficiently precise control.

Vitamin A as an Anti-infective Agent.—MELLANBY and GREEN (*Brit. Med. J.*, 1929, i, 984), in a preliminary communication call attention to the effect of vitamin A in raising the resistance of the body to bacterial infection. They observed that animals deprived of vitamin A died ultimately with multiple foci of infection, whereas control animals receiving vitamin A remained in good health. Animals which had

developed infective lesions, if given in time abundant vitamin A, usually recovered completely. On the basis of this observation, the authors undertook to investigate the effect of two preparations rich in vitamin A ("radiostoleum" and preparation Y) on puerperal septicemia. Of the 24 cases not receiving the vitamin A, 22 died; in the 5 cases receiving vitamin A there was no death, and all made complete recovery. It would appear that the effect of vitamin A is rather to increase gradually the general resistance than to act as a substance having a specific bactericidal or antitoxic effect. In all the 5 cases reported Streptococcus hemolyticus was cultured from the blood stream. There is reason to believe that the anti-infective action of vitamin A is not a specific in puerperal septicemia, and it is most probable that the same increase in bodily resistance would be found in many other types of infection. The body in times of special stress, as in pregnancy, should receive an adequate and large supply of vitamin A in form of natural food. Such foods include egg yolk, green vegetables, milk, butter and cheese. Cod-liver oil also contains vitamin A in abundance.

The Clinical Use of Acetyldimethylodihydrothebain.—The therapeutic effect of this derivative of thebain, commercially called "Acedicon," was tested on 1200 patients by BERTRAM and STOLTENBERG (*Klin. Wchnschr.*, 1929, **8**, 883). The drug was administered orally in doses of 0.005 to 0.01 gm., up to 0.01 to 0.03 gm. daily. The subcutaneously administered dose was 0.005 to 0.01 gm. The effect of the drug was identical whether administered by mouth or subcutaneously. In patients with pain the effect was less intense and of shorter duration than that of morphin. The authors do not feel, however, that this aspect of the problem is settled. In pathologic states associated with cough the drug exerted beneficial effect. In suppressing cough due to tracheitis and acute bronchitis, 0.01 gm. "acedicon" had a better effect than 0.03 gm. codein. In patients with pneumonia, and severe hiccough, the drug had no advantage over a number of other therapeutic agents. It was used successfully in cases with bronchiectasis and pulmonary congestion due to cardiac failure. In a number of patients, especially after larger doses, 0.01 gm., a soporific effect was noted. Depression of the respiration was not observed. In patients with dyspnea the air hunger was reduced. No untoward effect on the cardiovascular system was observed in normal subjects, or patients with cardiovascular diseases. Similarly, changes were not observed in the metabolism and body temperature. In 18 patients vomiting lasting for several hours occurred. Associated with this ataxia and signs of collapse developed. The authors advise to begin always with smaller doses (0.005 gm.). When the drug was used continuously the analgesic and soporific effect disappeared within a short time. The effect on cough lasted longer. There were patients with cough, however, who failed to respond after a prolonged use of the drug. Withdrawal symptoms were not observed with certainty. The problem of whether or not acetyldimethylodihydrothebain is a habit-forming drug cannot be considered as settled. In three morphin addicts "acedicon" proved to be a successful substituting agent. The authors believe that the effect of this drug is between that of morphin and codein, and closer to codein than to morphin.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Enuresis in Children.—MOHR and WATERHOUSE (*Am. J. Dis. Child.*, 1929, **37**, 1135) studied 15 children suffering with enuresis in a home, to determine the causes of enuresis, the response to a routine treatment, and the physical and mental differences between this group and a group of 15 normal children in the same home. They found that familial enuresis was common, several children in a family suffering with the disease, and the parents of some giving a history of enuresis also. The principal factors in the production of enuresis in these children seem to be poor training, emotional factors, physical factors, suggestion and fatigue. Enuresis in this group was frequently the result of poor training, many of the children had never learned the dry habit. Two cases were noted in which the control of the bladder had been acquired but with subsequent onset of enuresis. Physical comparison of the enuretic and control groups indicated that there was no relationship between specific physical defect and enuresis. The children with enuresis were relatively in poorer nutritional condition and of slightly inferior general physique. The children with enuresis had less efficient cardiovascular systems as measured by a cardiovascular efficiency test. Physical differences between the children with enuresis and normal children may be of the nature of constitutional variations. In this group the studies did not confirm the reports of other groups of a reversal of the normal relationship between concentration of urine voided during the day and that voided during the night. These enuretic children were emotionally less stable and betrayed a greater number of emotionally conflicting situations than did the normal group. The variety and combinations of causative factors ranging from purely organic to purely psychogenic were in keeping with the view that enuresis is frequently a symptom of neurosis. The therapeutic procedure was largely a limiting of fluid intake after 5 P.M.; sleeping on the floor without mattresses, on a rubber sheet; the cleansing of the sheets by the children themselves; the encouragement of the children by praising the dry nights. This resulted in complete relief in 4 cases and improvement in 7 others.

Cervicovaginitis.—STEIN, LEVENTHAL and SERAD (*Am. J. Dis. Child.*, 1929, **37**, 1203) recommend the use of the vaginoscope for the careful study and treatment of young girls with genital inflammation. Cervical involvement is an essential part of the underlying pathologic process in cases of so-called vulvovaginitis. This fact is appreciated after vaginoscopic study. The urethra also is frequently involved. Because of this fact, the authors recommend the term cervicovaginitis instead of vulvovaginitis. It was necessary to treat directly the cervix and the urethra in order to insure absolute cure. They found that about

one-fifth of their cases were of gonorrheal origin and they found that treatment with mercurochrome ointment was a simple and effective method. In all varieties of cervicovaginitis the duration of treatment with 1 per cent mercurochrome ointment in the patients with gonorrheal infection was eleven weeks, while those in whom infection was suspected and those in whom it was nongonorrheal were cured in less than one-half the time. There were recurrences of discharge after three months in about 20 per cent of the patients with gonorrheal infection, while there was no recurrence in those in whom the infection was nongonorrheal. A long period of observation using the vaginoscope after the cessation of the active treatment was required in order to determine the cure.

The Clinical Value of Sunlight Through Ultraviolet-transmitting Glass.—CALDWELL and DENNETT (*J. Am. Med. Assn.*, 1929, **92**, 2088) found that infants and children may be given sun baths of two or three hours daily throughout the winter, not as a substitute for ultraviolet-lamp irradiation for the cure of disease, but as a prophylactic measure. They found that there were ample ultraviolet rays in the antirachitic range in this latitude during the winter to be of definite value to those receiving them through a special type of window glass when exposures are made in the direct path of the sun's rays, since enough of these rays penetrate the glass to prevent rickets and spasmophilia in a normal properly fed baby. They also point out that the general impression that ageing of the glass decreases the therapeutic effect is erroneous.

Respiratory Disorders in Infants.—ABRAMSON and BARONBERG (*J. Am. Med. Assn.*, 1929, **92**, 2156) in this study attempted to lessen the incidence of these infections by putting into practice the principles of aseptic nursing. During the course of a winter all persons coming in contact with the infants in one ward were required to wear surgical masks and to scrub their hands thoroughly before the examination or handling of children. A comparison made with infants in a control ward where no such precautions were taken, showed that a decrease of respiratory diseases of only 10 per cent was accomplished by this means. The greatest difficulties arose from occasional infractions of technique on the part of the nurses as well as from the impossibility of preventing contact infections from child to child. Infants who were kept in cribs showed almost a 50 per cent higher incidence of respiratory disorders than those cared for in bassinets. The frequency of infection per child was less in the protected than in the control ward. They also found that aseptic nursing was of no value in preventing the spread of an outbreak of varicella.

The Care of Rheumatic Children.—FORDYCE (*Brit. Med. J.*, 1929, i, 146) observed 540 children in a special outpatient clinic for rheumatic children. Of these, 321 had apparently no permanent cardiac lesion, while 119 had established cardiac lesions but with satisfactory myocardial responses. There were 25 cases in which there was uncertainty

as to whether the cardiac injury was permanent or not. Cardiac lesions and failing heart were noted in 41 cases and 9 had acute rheumatic fever, 16 had congenital heart deficiency. There were 9 deaths from rheumatic carditis. Exclusive of cases of congenital heart disease and all cases of acute rheumatic fever, the outcome of which hung in the balance, and giving the benefit of the doubt in prognosis to all cases of doubtfully permanent cardiac lesion of 515 cases recommended to the clinic as rheumatic and accepted as such, 346 could be regarded as suffering from no permanent heart lesion, while 119 had permanent lesions, but showed good response and 41 showed evidence of failing heart muscle and 9 died. In other words, 50 children, or 10 per cent, had died or were unlikely to survive childhood, and 119, or 25 per cent, were permanently crippled to a greater or less extent. In the active care of the children the removal of infected tonsils was greatly stressed. Of the 531 rheumatic children, 130 underwent tonsillectomy in a hospital and 22 at a school clinic. Four cases were refused permission for operation by the parents and in 67 other cases operation was greatly needed. Thus, in 213 out of 531 children, or about 40 per cent, tonsillectomy was considered advisable. In none of the patients operated upon did unfavorable symptoms develop from the operation, regardless of how active the rheumatic symptoms were at the time.

Familial Purpura Hemorrhagica Without Thrombopenia.—ROTHMAN and NIXON (*J. Am. Med. Assn.*, 1929, **93**, 15) made a critical analysis of cases reported in the literature and comment that proper classification is extremely difficult. These cases did not correspond to any other well-known types of purpura. The purpuric manifestations associated with a normal platelet count and the heredofamilial factor of fairly constant observation, where such a considerable variation exists in the coagulation and bleeding times as well as in the clot-retraction phenomenon, the confusion is partly due to the lack of uniform laboratory methods for these determinations and also to the fact that a definite variation occurred in many of the individual cases at subsequent examinations. This condition must carefully be differentiated from other forms of purpura, especially from the rare case of familial Werlhof's disease and also from hemophilia and familial telangiectasia. The etiologic mechanism in this form of purpura is not clearly understood, but it has been attributed to a functional insufficiency of the platelet. The inability of the clot to retract may be due to the absence of the ferment retractozyme, or its presence in a less active form. Too much emphasis should not be placed on the ability of the clot to retract, as this phenomenon is not always constant in normal individuals. In some cases abnormalities in the size of the platelets and alterations in the protoplasms and granules have been found. Pyknosis and other evidences of degeneration are frequently met. Little can be said concerning the treatment employed. Blood transfusion has proved of great aid in tiding the patient over the severe attacks of bleeding. Roentgen ray irradiation of the liver and spleen is of doubtful value. In patients bleeding from the nose, the hemorrhage was diminished by cauterization or removal of tonsillar tissue. As regards removal of the spleen, the value of this is not settled at the present time.

The Clinical Significance of the Water of Metabolism in Children.—GOLDSTEIN (*Arch. Ped.*, 1929, **46**, 371) states that the water of metabolism is a very important factor and is of great clinical significance in children in health and in diseased conditions. Diet modifies water balance to a great extent. Carbohydrates and proteins favor water retention but in excess, especially if the protein is over 20 per cent of the total calories. Metabolism and water loss is stimulated with a subsequent loss in weight. If carbohydrates are less than 3.5 per cent in the diet, acidosis may result. A high-fat diet encourages water loss and, indirectly, weight loss. In severe cases of vomiting with great loss of water and hydrochloric acid there may develop a retention of alkalies and an alkalosis. There is no question but that marked changes in the water balance cause the same influence to partly change the alkaline reserve. Fortunately, the latter content of the plasma is easily compensated and is, therefore, more or less constant.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Surgical Treatment of Uterine Prolapse.—The number of operative procedures which have been recommended for the surgical cure of uterine prolapse is so large that it is often difficult to decide which procedure should be employed. Of course, the real gynecologist will vary his procedure to meet the conditions present in the individual case. The preferences at the Mayo Clinic have been detailed by MASSON (*Minn. Med.*, 1929, **12**, 67), who states that during the childbearing period, repair of lacerations and shortening of the round ligaments should be performed. External shortening of the round ligaments of the Alexander type is now seldom advised. Opening the abdomen adds little if any risk to the operation and often other surgical conditions within the abdomen can be attended at the same time. He prefers the modified Gilliam type of operation, shortening the round ligaments through the internal ring, but he has also found the Baldy-Webster operation satisfactory. If a raw surface is to be left on the anterior uterine wall as the result of the separation of adhesions or myomectomy, the Coffey type of anterior plication of the round and broad ligaments is satisfactory. If a raw surface exists on the posterior surface of the uterus, posterior plication should be performed. If women are close to or have passed the menopause, and slight prolapse and troublesome cystocele or rectocele exist, he advises the Watkins

interposition operation, ligating the tubes if necessary and repairing the pelvic floor. In many cases, especially before the menopause, the uterus is too large for this procedure, and if the regular technique is followed the patients complain of a bulging in the introitus. To overcome this, it may be advisable to reduce the size of the uterus by removing part of it. A wedge-shaped piece can be removed from the fundus and the cervix can be amputated, but the author prefers to remove all of the anterior wall and thoroughly denude all the mucous membrane from the uterine cavity and cervix, cutting a wedge-shaped piece from the fundus on each side at the site of the entrance of the Fallopian tubes. Bleeding is controlled by suture and the resulting uterine tissue, less than half the size of the original organ, is sutured under the bladder in the regular way. This operation deserves special mention as it effectually cures the cystocele, eliminates the danger of carcinoma and prevents troublesome and dangerous sequelæ, such as distortion of the bladder base or anterior vaginal wall and the possibility of pregnancy. The Mayo operation for cystocele and prolapse is especially suited for the case in which a large cystocele and marked prolapse are present. In cases of marked prolapse with a relatively small cystocele, good results are obtained by performing perineorrhaphy and fixing the uterus to the anterior abdominal wall. In cases of extreme prolapse it is sometimes advisable to perform subtotal or total hysterectomy and anchor the vault of the vagina into the abdominal wound. It is sometimes advisable in elderly patients with a prolapse and large cystocele and rectocele to denude the mucous membrane on either side of the vagina from the introitus to the cervix and approximate these raw surfaces, leaving two narrow mucous tracts or canals to take care of any discharge from the uterus. If a vaginal hernia develops following a hysterectomy it is sometimes necessary to obliterate the vagina completely by first removing all the vaginal mucous membrane and closing the opening by multiple circular sutures, commencing at the top and working down to the introitus, simply leaving room for the urethra under the pubis.

New Technique for Lipiodol Injection of the Uterus.—In the simplified technique which ADAIR and MCDONALD (*Minn. Med.*, 1929, **12**, 146) have developed for injecting lipiodol into the uterine cavity, the Rubin cannula is no longer used. Instead a rubber mushroom or retention catheter is inserted into the uterus by means of the regular mandrin used for the insertion of retention catheters. The anterior lip of the cervix is held with a tenaculum for convenience while placing the catheter but is released before the Roentgen ray exposure is made. The catheter is then drawn down so that the bulb or mushroom tip rests firmly over the internal os. Lipiodol is then injected and the plates made. In a few cases there has been a small reflux of lipiodol along the sides of the catheter into the vagina but this occurs only in the cases of multiparous women with more or less patulous cervices and has been noted also in similar cases where the cannula has been employed. Aside from the simplicity of the method, the chief advantage is that instruments are not visualized in the hysterogram to interfere with the more accurate reading of the conditions represented in the picture.

Conservative Treatment of Pelvic Endometriosis.—According to WHARTON (*South. Med. J.*, 1929, **22**, 267) every surgeon has to answer the following question when operating upon a case of pelvic endometriosis: Can I save the functions of menstruation and childbearing or is it necessary to remove the uterus, tubes and ovaries? His answer is that it is desirable to treat these cases conservatively in young women and when the conservative treatment is successful, the end result is well worth while. In his experience, such patients have conceived and for periods of six years have remained in perfect health. If one can be reasonably sure that the ovaries can be stripped completely of endometrial growths, if the uterus can be left in a healthy state and if the pelvic organs can be left in normal positions, then one can attempt conservatism with a fair chance of a gratifying result. In his experience, in patients over thirty-five years of age, the pelvic disorders are so grave that conservatism is unwise. Also when both ovaries and the uterine wall are involved in endometriosis, conservative measures are very risky. This seems to us to be very sane advice and will undoubtedly be of help in reaching a decision when confronted with these interesting lesions.

OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.,
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Retinal Detachment Complicating Insulin Therapy (A Biophysicochemical Explanation).—ALPERIN (*Am. J. Ophthal.*, 1929, **12**, 486) reports 1 case and has seen 2 others in which detachment of the retina appeared to be related to insulin therapy. The patient had suddenly gone blind in the right eye, with nothing unusual in the history but a vague, dull pain in the parietal region. The retina was hazy; there was no light perception. Diet was restricted and insulin withdrawn. The detachment of the retina gradually decreased and vision was recovered. In explanation, the author advances the theory of change in osmotic pressure causing changes in intraocular pressure. For any one of a number of reasons, hypoglycemia may occur in diabetic patients. The osmotic pressure is in direct proportion to the degree of ionization of the dissolved substances in the blood (electrolytes, such as mineral salts), and this is in direct proportion to the dilution of the electrolyte. Consequently, the thinner the solution, here the blood, the more molecules of the electrolyte will dissociate into ions and the greater the osmotic pressure in the hypoglycemic blood. Under such conditions it would be possible for fluid to pour into the eye through the congested ciliary vessels increasing intraocular pressure and producing the symptoms of acute glaucoma (Richter) or it could pass into the subretinal

space from the choroidal plexus, resulting in detached retina. The fundamental biophysicochemical changes are, in the author's mind, the same. The author recommends that the eye grounds of diabetic patients be examined from time to time, and if visual disturbances occur, that insulin be discontinued temporarily.

Ocular Residua and Sequelæ of Epidemic Encephalitis.—Barlow (*Arch. Ophthal.*, 1929, **1**, 501) reports that ocular phenomena play an important rôle in epidemic encephalitis, appearing in the early stage, when they are usually transient and disappear in a few days or weeks, or in the postencephalitis or Parkinsonian stage. The third and sixth nerves are most frequently affected and occasionally the trochlear. The optic nerve is rarely involved; optic neuritis and papilledema are rather infrequent occurrences even in the early stages. The British Ministry of Health has stated that "In the diagnosis of lethargic encephalitis a negative sign of value in the absence of optic neuritis." Ophthalmoplegia is of frequent occurrence, appearing in two forms, peripheral and nuclear. The peripheral form always recovers; the nuclear may clear up if it is slight, but if more severe it always leaves some permanent paralysis. It may involve any part of the nuclear mass. Oculogyric crises occur most frequently, if not exclusively, in the Parkinsonian syndrome. Muskens has localized the lesion just in front of the posterior commissure, one of his reasons being that there is a frequent association of tonic lateral position of the eyes with the upward or downward position. The two bundles involved in these two forms of forced movement are close together only at one point—just in front of the posterior commissure. Nystagmus is frequently observed as a late symptom. It is of greatest diagnostic value when it is up or down, the lateral being present in numerous other diseases. Convergence paralysis is considered by many to be one of the most frequent eye symptoms in the Parkinsonian syndrome. This, however, requires differentiation between congenital and acquired convergence paresis. Paresis of accommodation, less frequently a complete paralysis, is one of the earliest eye symptoms and is frequently observed as a late complication. Formerly this was considered as a complication of diphtheria only. The pupil has proved of little value for it is extraordinarily inconstant. Argyll-Robertson pupil has been frequently observed in acute encephalitis, but is a rare occurrence in chronic encephalitis. There is another symptom of the eyes in the postencephalitic Parkinsonian stage in which the eyeballs are peculiarly rigid, but in which there is no paralysis of the eye muscles. The eyes can be moved with effort if the patient be aroused. Cords has designated it "myostatic rigidity of the eyes." The face has a masklike expression, the action of the facial muscles is entirely abolished and the eyes are expressionless, staring into space for hours at a time.

Investigations on the Toxic Action of Trichlorethylene, Particularly on the Eye.—Meyer (*Linn. Monatsbl. f. Augenh.*, 1929, **82**, 309) reports that various injuries to the eye, such as a black fleck on the fovea centralis, absence of the corneal reflex, insensitivity of the cornea, absence of the secretion of tears, irritation and swelling of the conjunctiva, double vision, swelling of the ocular fundus, dyschromatopsia,

retrobulbar neuritis have been reported from industries and professions as due to trichlorethylene. Unfortunately, in most of the cases an adequate physical examination had not been made and in many of the cases the possibility of the concomitant action of other toxins, such as alcohol, could not be excluded. It is also possible that decomposition products of trichlorethylene may have caused the damage, since it decomposes in contact with metals, particularly iron. Late injury to the eye had never been reported. The author, in his experimental investigations, used 5 dogs, anesthetizing 2 repeatedly, giving the trichlorethylene subcutaneously in the other 3. Under deep anesthesia the corneal reflex was absent and the pupils were usually medium in width and always reactionless. In no case was there a change in the ocular fundi. Subcutaneous injection began with 1 cc. and increased at the rate of 2 to 3 cc., until the 3 animals had received 45 cc., 56 cc. and 30 cc. respectively. At autopsy, no changes were found in the retina and histologic examination of the optic nerve, carried to beyond the chiasma, was entirely negative. Further investigations on apes, in the author's opinion, might be advisable since Roemer has shown that reactions of the optic nerve of certain species are not the same as in man.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

The Physiology of Vestibular Nystagmus.—Vestibular nystagmus is an intricate physiologic phenomenon, which is important as an aid in neurologic and otologic diagnosis, and as a test of fitness in aviation. In outlining the present status of the knowledge of the physiology of vestibular nystagmus, IVY (*Arch. Otolaryngol.*, 1929, **9**, 123) summarizes as follows: "On stimulation of the nonacoustic labyrinth, movements of the eyes occur which are compensatory in nature. The movement of the eye is characterized by a slow movement called the deviation, or slow component, and a quick movement opposite in direction to the deviation called the nystagmus, or quick component. The deviation of the eyes is due entirely to stimulation of the labyrinth. The nystagmus is most probably due to a reflex *via* the muscle centers of the eyes which is excited by the stimulation of kinesthetic sensory nerve endings in the muscles of the eyes, and is not due to a cerebral reflex arc. The cerebrum exercises its well-known inhibitory control over this reflex. It is pointed out that the cristæ of the canals are most probably not stimulated by the inertia effect of canal currents, and that Maxwell's theory, which holds that the cristæ of the ampullæ are stimulated by changes in tension of the utricular membrane caused by inertia effects

in the larger bodies of fluid in the vestibule and utriculus, is more reasonable and probable. It is shown that a correlation exists between the type of nystagmus that results from rotation in the various visual planes in the dog-fish and in man."

The Clinical Significance of Spontaneous Nystagmus.—Because its anatomic basis is best known, spontaneous nystagmus is the most important symptom produced by the labyrinth. Inasmuch as it can be produced by various organs, the clinical evaluation of spontaneous nystagmus is often difficult. Otologically, spontaneous nystagmus can be divided into a labyrinthine, and a nonlabyrinthine, type, although the pathogenesis of nonlabyrinthine nystagmus is obscure in many respects, so that diagnostic conclusions based on this type of nystagmus are as yet hardly possible. In order to differentiate between labyrinthine and nonlabyrinthine nystagmus, BRUNNER (*Arch. Otolaryngol.*, 1929, **9**, 1) utilizes the following points: (1) *Dizziness*—labyrinthine nystagmus is always accompanied by labyrinthine dizziness (turning dizziness, tactile dizziness); (2) *Association of Eye Movements*—spontaneous labyrinthine nystagmus always exhibits associated eye movements; (3) *Form of Nystagmus*—spontaneous labyrinthine nystagmus, in its typical form, is combined horizontal and rotatory, or only rotatory. Diagonal spontaneous nystagmus is practically always, and vertical spontaneous nystagmus is often, of nonlabyrinthine origin; (4) *Inversion of Experimental Optical Nystagmus*—as elicited by means of the author's revolving umbrella. Normally, and in persons with spontaneous labyrinthine nystagmus, the "umbrella test" causes a coarse horizontal nystagmus in the direction opposite to that in which the umbrella is turned, whereas in those with spontaneous nonlabyrinthine nystagmus several abnormal reactions may occur, which can be grouped under the term "inversion of experimental optical nystagmus." In order to render this "inversion" clearer, Brunner cites 10 illustrative cases, giving the findings of the various functional tests of the labyrinth.

A Comparison of the Outlines of the Frontal Sinus in Vivo as Shown by Transillumination and the Roentgen Rays.—By indicating with opaque paint on the skin the apparent contour of the frontal sinuses in a small group of medical students, as revealed by transillumination, and then taking radiographic films of the same sinuses, FETTEROLF and SPRENKEL (*Arch. Otolaryngol.*, 1929, **9**, 181) found that the frontal sinuses were decidedly smaller than they appeared to be on transillumination, the Roentgen ray films showing their upper margins to be from $\frac{1}{2}$ to $\frac{3}{4}$ inch lower than the impression conveyed by transmitted light.

"A Working Hypothesis for Research in Otosclerosis."—YATES (*Ibid.*, p. 852) reasoning from results of his clinical and audiographic investigations, believes that clinical otosclerosis is at times the terminal stage of subacute otitis media in which the products of inflammation of the middle ear are carried away by the Eustachian tube.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Acute Massive Collapse (Atelectasis) of the Lung.—Acute massive collapse (atelectasis) of the lung, states BOWEN (*Am. J. Roent. and Rad. Ther.*, 1929, **21**, 101) is a definite clinical entity characterized by more or less airlessness of a lobule, part or all of a lobe, a whole lung or even of both lungs. Although described with surprisingly few errors more than seventy-five years ago, it has in recent years been rediscovered as a postoperative complication. It is rarely seen without some measure of increased or retained secretion which may be excessive and which rapidly becomes purulent. The most important premonitory symptom is a moderate elevation of temperature; the most notable subjective sign is dyspnea, and the most reliable physical and Roentgen finding is displacement of the heart toward the affected lung.

Much of the discussion as to its etiology is still on a theoretical basis. It has been attributed to paralysis of the diaphragm or a part of it, to fixation of the diaphragm by pleuritis or traumatism to the upper abdomen, to reflex action from injury of the vagus, and to plugging of a bronchus with mucus. Bowen inclines strongly to the theory of plugging by mucus. He also regards the pre-anesthetic administration of morphin and atropin as a predisposing factor, and he thinks that general anesthesia cannot be absolved from all suspicion as an etiologic factor. Patients experiencing the so-called "wet anesthesia" should be watched with especial care during the early postoperative period in order that no premonitory sign of collapse shall be missed.

The condition may be massive, involving a lobe or lung, or partial, lobular or patchy. Accordingly attacks may be fulminant, moderate, latent or evanescent. In by far the greater number of cases a rise in temperature is the first symptom of impending collapse. It rarely exceeds 102° F. Any rise of temperature after the postoperative reaction is over should suggest the thought of atelectasis. In the fulminant type the face is suffused and the expression anxious; dyspnea is urgent and there is marked diaphoresis; the patient complains of a sense of tightness amounting to real intrathoracic pain. Commonly a sense of equilibrium is established within a few hours and the course is thereafter less urgent. In severe cases, on inspection, it may be noted that the patient does not lie straight in bed but the affected side of the thorax is contracted and fixed, and the shoulder is depressed toward the hip. Auscultatory signs vary from an entire absence of breath sounds over a wholly collapsed lung, to many râles in adjacent unaffected portions of

the lung. The heart is displaced toward the affected side in ratio to the extent of atelectasis.

In the roentgenogram the density of the affected area is marked and fully as great as that seen in lobar pneumonia; and lobar or bronchopneumonia is likely to enter into the differential diagnosis. Due regard for the other signs, particularly cardiac displacement, should make the diagnosis clear.

The duration of the condition varies from a few hours to four weeks. There are no specific remedies and the use of drugs, if any, must be on the expectant plan. Sante has noted spontaneous reinflation when the patient was rolled back and forth on the uninvolved side; Gairdner, seventy-five years earlier, reported a case of collapse which disappeared under an emetic and forced decubitus on the opposite side. Bowen admits the merits of Sante's procedure but doubts that it will prove a panacea for all cases. Bronchoscopic drainage now has 14 successes to its credit, with no actual failures, and the outlook for this method is promising.

Nature of Arthritis.—A fifth of all cases of arthritis, especially those which are atrophic in type, show a slight decrease in metabolism, according to PEMBERTON (*Radiology*, 1929, **12**, 235). Metabolism of nitrogen, fats, calcium, phosphorus and uric acid seems normal, but there is a delayed removal of ingested glucose from the blood which closely parallels arthritis and focal infection. Coincident with this there is a delay in the utilization of oxygen, at least in the smaller vessels, due to a vasoconstriction, or a similar change, inducing a sort of anemia in certain structures. A study of the capillaries of the arthritic by Lombard's method of direct microscopic observation, shows that they contain on the whole less blood than normal, and that the stream tends to be sluggish and interrupted. These phenomena help to explain the beneficial effects of physiotherapeutic measures, notably exercise, massage and heat, all of which are widely used by the laity. Both exercise and external heat increase the circulatory rate, as shown by a sharp rise in the oxygen percentage saturation of the peripheral blood; they also induce an increase in the red cell count. The influence of massage in increasing the circulation is not so evident, but it does, nevertheless, have a very marked effect on the red cell count.

Rôle of the Roentgen Ray in Determining the Resectability of Gastric Cancer.—Underlying all factors affecting resectability, in the opinion of MOORE (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 226), are three of basic importance, namely, the situation of the gastric cancer, the presence or absence of fixation to adjacent structures, and the presence or absence of metastasis. By demonstrating the seat and extent of the growth the Roentgen ray renders its greatest service. Cancers in the cardiac third of the stomach are seldom accessible for resection, while those in the pyloric third are readily resectable so far as situation alone is concerned. In general, cancers confined to the lower half of the stomach, *i. e.*, distal to the incisura angularis, can be excised, but those which involve the upper half are not resectable. If the cancer is of the scirrhous, infiltrating type, an allowance of 2 or 3 cm. beyond the invasion shown in the roentgenogram should be made. When attachment

to the pancreas, mesocolon, liver, omentum, colon or abdominal wall is firm, resection is likely to be impossible. If fixation is not obvious, it is always to be surmised when a cancer is extensive or when the palpable tumor greatly exceeds the defect in the gastric shadow. Concerning metastasis the Roentgen ray yields scant information. Metastasis to the lungs or bones is readily demonstrable, but occurs very rarely from cancer of the stomach. Metastasis to the liver and abdominal lymphatics is common, is not discoverable with the Roentgen ray, and often makes resection futile. On the whole, the interdict of the Roentgen ray against operation deserves and receives respect, while its assent to operation is merely conditional and subject to unavoidable error.

Treatment of Carcinoma of the Rectum.—Sixty-five cases of carcinoma of the rectum are reported by JONES (*Am. J. Roent. and Rad. Ther.*, 1929, **21**, 168) in which treatment was by Roentgen and radium irradiation. In 10, or 15 per cent of the total number, the patients are well, having remained so for periods varying from three to seven years. Although the treatment of choice for an operable cancer of the rectum is operation by the combined abdominoperineal routes, if operation is refused or the condition is inoperable there is sufficient evidence that a cure can be obtained in certain cases and marked palliation in others by the combined use of radium and Roentgen rays.

Massive Hemorrhage from the Gastrointestinal Tract.—SANTE (*Am. J. Roent. and Rad.*, 1029, **21**, 144) reports 2 cases of severe hemorrhage from the gastrointestinal tract in which no ulcer, cancer or other organic cause could be found. Many cases of bleeding have been reported by others in which the point of bleeding could not be demonstrated. Explanation of the hemorrhage merely on the basis of seepage from engorged vessels has never seemed entirely satisfactory. Experimental work of Auer has suggested the possibility that the hemorrhage is a manifestation of autoreinoculation of a person previously sensitized by infection of the gall bladder, appendix or diverticulum of the intestinal tract with a resulting localized anaphylactic reaction. Sante reasons, therefore, that all patients having hemorrhages without any demonstrable organic lesion should be subjected to thorough examination for protein sensitization and for focal infection of organs which drain into the intestinal tract.

Technique of Gall-bladder Examinations.—PILLMORE (*Am. J. Roent. and Rad. Therap.*, 1928, **20**, 539) has examined the gall bladder in 150 cases by making one film at full inspiration and another at complete expiration. He has found that at full inspiration the gall bladder usually moves downward and toward the midline of the body. At expiration the reverse occurs. The greatest movement is in tall thin persons and the least in stout individuals. Inspiration and expiration films frequently aid interpretation by shifting the gall bladder into a position where it is more readily visible, and by moving it away from areas of gas in the bowel.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

A Case of the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas, with Pathologic Examination.—De Bruyne and Ruby O. Stern (*Brain*, 1929; **52**, 84) were able to find only 12 cases previously reported in the literature with histologic verification. Besides these they found 14 clinical records, 6 of which they consider as of doubtful value. These cases are summarized by the authors. They also review the discussions of the pathology and call attention to the fact that the essential lesions appear to be hypertrophy of the peripheral nerves, ganglia, and spinal roots, depending on 2 factors—one an increase in the interstitial tissue; the other, which is peculiar to the disease, a proliferation of the cells of the sheath of Schwann with a concomitant demyelination of nerve fibers. There is also an associated degeneration of the posterior columns of the spinal cord, the relation of which to the lesions in the nerves and the nerve roots may be consecutive, though this has not yet been definitely decided. They present a case examined by them clinically and pathologically. Gross examination at autopsy showed atrophy of the muscles of all four limbs, more noticeable distally than centrally. The peripheral nerves could be palpated, were somewhat larger than normal and excessively firm. The nerves were greater close to the ganglia and smaller peripherally. Nerves proximal to the ganglia did not appear much enlarged but the ganglia themselves were greatly increased in size up to the sixth cervical and there was some difference in size on the two sides. On section the nerves resembled a tendon. Microscopically the nerves showed practically all of their fibers to be swollen and there was an excess of nuclei. Between the nerve fibers and separating them lay masses of non-nucleated substance which stained deep yellow with van Gieson's counter stain. These masses were more numerous in the proximal portions of the nerves, whereas degeneration of myelin was more evident in the distal portions. The authors believe these masses to originate in hypertrophy of the sheaths of Schwann. They fail to find any of the "onion bulb" masses which are supposed to be characteristic. They designated the homogeneous masses as "plastic swellings." Scharlach R. preparations showed a small amount of fat in the swellings. The interstitial tissue was also hypertrophied and the bloodvessels in the nerves were thicker than normal, the adventitia especially being involved. The spinal ganglia revealed similar lesions but the interstitial hypertrophy was not so great. The authors believe that in these preparations they could trace the

origin of the substance from cells of the sheath of Schwann and they found the usual degenerative changes in the ganglion cells. The nerve roots were well myelinated and showed only very early plasmatic swellings. The cauda equina showed more extensive lesions than the other nerve roots. The spinal cord showed degeneration in the posterior columns only in the very lowest segments. Anterior horn cells in the cervical and lumbosacral enlargements showed a few cells displaying signs of central chromatolysis. The muscles showed irregular atrophy and the vessels were slightly thickened. The authors call attention to the similarity of their case to the original descriptions of Dejerine and Sottas. The presentation is a polyneuritic symptom picture with wasting, weakness and sensory loss of peripheral distribution. Pupils small and reacting sluggishly to light. (The authors consider the Argyll-Robertson pupils in the second case of Dejerine and Sottas to have been due to the lues.) Course fibrillation and partial R. D. were present as was lancinating pain. Family histories and clinical courses were very similar. The authors stress their belief that the myosis observed in most cases in the literature is due to involvement of the cervical sympathetic fibers in the first thoracic roots. The great difficulty of detecting the hypertrophy of the nerves during life is emphasized. "Thus of the two signs which have come to be regarded in some of the modern textbooks as characteristic of the malady, one, the Argyll-Robertson pupil, is shown to have no value; the other, hypertrophy of the accessible nerves, may be inconspicuous, and may be observed only if especially looked for."

Psychology and Psychiatry in Industry. The Point of View of a Psychologist.—VITELES (*Mental Hygiene*, 1929, **13**, 361) believes that psychology has much more to offer industry than has psychiatry. He holds that the development of psychology along empirical laboratory and experimental lines has lead the psychologist to a scientific viewpoint that is lacking in the psychiatrist. He cites a large number of contributions which psychology has made to the understanding of accidents, the effect of monotony on production, the training of workers and so on, to show that the method of psychology is objective. He states that, "The psychiatrist still leans heavily upon uncontrolled conditions; upon observations not subjected to careful measurement; upon interpretations of mass data that may be too largely influenced by a point of view, representing rather the bias of the individual worker than a general principle subjected to verification through controlled observation of random, unselected samplings." What he considers the ineffectiveness of psychiatry in industry, he believes to be due to the carrying over into normal relationships the viewpoint acquired by prolonged contacts with abnormal patients. He calls attention to the fact that it is only very recently that psychiatry has had any dealings with the normal, whereas psychology has concerned itself from the outset in attempts to understand normal people and normal behavior. (One gathers from the entire article that while the author's criticisms are unquestionably just to some extent, he has missed the essential point of the application of psychological and psychiatric approaches to industry. One would not expect the two sciences to make the same contribution and his spirit of rivalry and jealousy is unfortunate.)

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D.,
PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Contributions to the Study of the Action of Ultraviolet Rays on Experimental Tuberculosis of the Guinea Pig.—NASTA and BLECKMANN (*Arch. roum. de pathol. exper.*, 1928, **1**, 353) have demonstrated in guinea pigs, infected with experimental tuberculosis, a diminution in sensitivity to the intradermal tuberculin reaction, which was very marked for the irradiated skin areas, yet distinct in those regions not directly exposed to the rays. The general response was also less when tuberculin was injected intraperitoneally, although attended by a febrile reaction. Large doses of tuberculin which killed the control, nonirradiated animal in less than an hour were not fatal to the irradiated guinea pig. These differences of reaction were absolute only for the early stages of the disease. The tissue-defense reactions following the reinoculation medium doses ($\frac{1}{5000}$ to $\frac{1}{50}$ mg.) of tubercle bacilli appeared to show an activation in the irradiated animals, where the resultant abscess appeared earlier and was more rapidly replaced by a fibrous healing nodule. In one instance, a second reinoculation with large doses ($\frac{1}{10}$ mg.) of tubercle bacilli resulted in only slight edema and transitory abscess formation with complete healing in the irradiated guinea pig, whereas the nonirradiated animal showed ecchymoses and subsequent formation of a nonhealing slough. A moderate and lesser leukocytosis and less accentuated polynucleosis, compensated by a slight increase of lymphocytes, were the characteristics which distinguished the blood picture of the irradiated tuberculous guinea pigs from that of the nonirradiated, tuberculous controls. A certain retardation in the progress of the lesions, with a longer span of life was observed in the irradiated tuberculous animals, compared with the nonirradiated controls. In view of their results, the authors feel that certain at least of the reactions known as allergic are neither the active factors nor in all cases the real indicators of the immune state.

Races of Meningococcus and Antimeningococcus Serum Therapy in Roumania.—NICOLAU (*Arch. roum. de pathol. exper.*, 1928, **1**, 155) has reported the bacterial incidence, together with the methods and results of serum therapy of an epidemic of cerebrospinal meningitis, attacking Bucharest during the winter of 1922–1923. The method of isolation of the meningococcus which proved most satisfactory, consisted in sowing directly the cerebrospinal fluid, or the residue of its centrifugation on solid media (gelose-ascites, gelose medium of T. Nicolle). As determined by agglutination tests in 33 cases studied,

the races of meningococcus were represented in the proportions of types A, 70.7; B, 25.0; C, 0.0; D, 4.3 per cent. In the treatment of the cases, antimeningococcic serum was injected into the spinal canal, the meninges, or the lateral ventricles, the injections being continued each day until the cytobacteriologic examination of the spinal fluid showed the desired picture. This consisted in diminution of the polymorphonuclear leukocytes; a normal appearance of the remaining leukocytes, with the absence of nuclear changes; absence of meningococci or very rare intracellular microbes. The continuance of the treatment beyond this point results in signs of meningeal intolerance. The clinical course is not a sufficient guide as to the course of serum therapy. In a total number of 35 treated cases, of which 9 were infants, 6, that is 17 per cent, died. The mortality for untreated cases in Roumania is 64 per cent. The author emphasizes the value of suspending serum therapy at the indicated time, the introduction of the serum in direct contact with the lesion and the use of interventricular injections in the fatal meningoventriculitis of infants as important aids to the reduction of the mortality of the disease.

Appearance of a Desensitizing and Hypotensive Substance in the Organism after Blockage of the Reticuloendothelial System.—MOLDOVAN (*Arch. roum. de pathol. exper.*, 1928, **1**, 167) has studied the functions of the reticuloendothelial system in experimental animals during the state of blockage of the endothelial cells, caused by the accumulation of granular material in their protoplasm following the injection into the circulation or peritoneal cavity of various substances, such as trypan blue, lithia carmin, colloidal metals and india ink. The experimental blockage of the reticuloendothelial system was followed after an hour, by the appearance in the circulation of a substance, which, when injected into sensitized guinea pigs, immediately before the administration of the intoxicating dose, protected them from anaphylactic shock. This desensitizing substance persisted in the circulation of the injected animal for a period of fourteen days. The active substance of the serum could be isolated chemically without impairing its activity. It proved thermoresistant, stable, soluble in acids, alcohol and water, dialysing readily across collodion membranes which did not permit the passage of protein substances. It was possible to titrate the protective dose of the isolated principle in a series of sensitized guinea pigs. The author regards this desensitizing substance as a product of internal secretion of the reticuloendothelial system. The serum obtained by the method of blockage possesses also a hypotensive action, which does not always run parallel with the antianaphylactic property. Sera containing the latter principle have been used with some success in clinical cases of hypertension where their administration was attended by a fall of blood pressure, occurring in five minutes, reaching its maximum in thirty to sixty minutes, and prolonged in effect for two to twenty-four hours.

The Arterial Supply of the Kidney in Nephritis.—BAEHR and RITTER (*Arch. Path.*, 1929, **7**, 458) have been able to demonstrate by injection methods a very considerable reduction in the smaller arterial and arteriolar divisions of the vascular tree in chronic diffuse nephritis.

They consider the inflammatory changes in the vessels to be relatively important in the production of the final contracted state of the organ. The study of four cases of early diffuse glomerulonephritis failed to reveal as yet any gross alterations in the arterial supply of the kidney.

Experimental Paratyphoid Infection by Mouth under Various Living Conditions.—Many attempts have been made to explain the outbreaks of paratyphoid epidemics in summer and autumn and also the infections following mild intestinal inflammations. In the pursuit of some explanation of these facts certain conditions controlling the pathogenicity of paratyphoid bacilli by feeding them to mice, rats and guinea pigs were determined by SEIFFERT (*Arch. f. Hyg. u. Bakteriol.*, 1929, **101**, 117). The pathogenicity was found to depend on two components: the ability to colonize in the intestine and the ability to pass through the intestinal wall. He considered the intestine the most important portal of entry, although highly virulent germs may establish infection from the oral cavity. The development of these bacteria in the intestine is helped if the animals are kept at temperatures of 28° to 32° C. and further, paratyphoid strains which disappear normally are thus enabled to become established. The second component which makes possible the parenteral invasion is favored by noninfectious inflammation of the intestinal mucous membrane (by feeding bile) or by raising or lowering the surrounding temperature, but changes in the food had no influence. The invasion depends on the injury of the mucous membrane by the germs which are pathogenic by feeding and apparently at ordinary temperature this injury is not enough to permit the invasion of the ordinary intestinal flora which does occur, however, if the surrounding temperature is kept high long enough. Paratyphoid bacilli can on occasion enter the tissues in a few hours and are recoverable from the mesenteric glands, liver and spleen. The outcome of the infection depends upon the virulence of the strain, and the defence power of the body. This latter can be raised by stimulating the reticuloendothelial system. The body is able to render the bacilli harmless not only by destroying them but also by changing them into weakly virulent forms.

Vaccination against Tuberculosis with Bacillus Calmette-Guerin.—This paper by RANKIN (*Canadian J. Res.*, 1929, **1**, 48) covers work on B. C. G. vaccine carried on in Alberta over a period of approximately four years, during which time some 250 calves were made the subject of experiments. The vaccine was found to be entirely harmless, vaccinated calves developing normally and showing at autopsy no tuberculous lesions. Vaccinated animals in most cases reacted subsequently to the tuberculin test. Calves vaccinated with B. C. G. and immediately exposed to infection showed moderately increased resistance to tuberculosis over unvaccinated controls. Calves vaccinated with B. C. G. and subsequently kept under sanitary conditions for a period, in order to permit resistance to develop before exposure to infection, showed 80 per cent immunity as compared with 14 per cent for the controls. The tuberculous lesions found in vaccinated calves were in general much less pronounced as well as less numerous than those in unvaccinated animals.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

The Causes of Illness at Different Ages. Hagerstown Morbidity Studies No. VII.—SYDENSTRICKER (*U. S. Pub. Health Rep.*, 1928, **43**, 1067), in a study at Hagerstown, Maryland, found that the respiratory diseases are the highest at all ages, and the highest point of this group is reached in the early years of life, declining rapidly to about the age of twenty years and then gradually increasing. Infectious diseases fall rapidly from the earliest years of life. From twenty-five years on they are a minor factor. In old age, organic diseases of the circulatory, nervous and urinary systems predominate. Adolescence and young adult life are the most favorable periods as regards nearly all classes of disease.

The Epidemiology of Undulant (Malta) Fever in Iowa.—HARDY (*U. S. Pub. Health Rep.*, 1928, **43**, 2459) has collected clinical, laboratory and epidemiological data on undulant fever. The diagnosis was based on serologic tests confirmed by clinical findings. The latter were, briefly, as follows: Insidious onset, weakness, profuse night sweats, chilliness, and rigors in some cases. Headache, backache, and joint pains were common. Constipation was the rule. The temperature was irregular and intermittent, usually with morning remissions often to normal. Only about one-third of the cases gave definite undulations with periods of freedom from fever. There was progressive loss of weight and anemia. The usual complications of undulant fever were observed. The diagnosis has been established in 83 cases in Iowa in a period of a little over one year. They were widely distributed throughout the state; twice 2 cases occurred in the same family. The largest number of cases occurred among farmers or persons living on farms. The number of males was 63 and the number of females 20. If one takes the cases that had no contact with live stock these are found to be equally divided between males and females. The cases occurred chiefly between the ages of twenty and fifty years. Hogs and cattle appeared to be the chief sources of infection; some cases seemed undoubtedly to be due to the use of milk from abortus infected cattle, others were clearly due to handling of infected stock, cattle or hogs, and one small group occurred among packing-house employees and seemed to be due to handling of infected slaughter-house products.

The findings are compared with those of Madsen, of Denmark, who found 122 cases of undulant fever among 2500 samples of blood examined which had been sent in primarily for the Widal test. In both series of cases children are strikingly immune, a fact difficult to reconcile with the theory that any considerable number of cases are due to the use of infected milk.

The Pathogenicity of Morgan's Bacillus: A Series of Thirteen Cases Attributable to Infection with this Organism.—Ever since the discovery of Morgan's bacillus in 1905 (*Brit. Med. J.*, 1906, i, 908) its significance has been uncertain. Morgan attached some importance to it as a cause of summer diarrhea, although he could demonstrate no antibodies in the patients' serum nor could he show that the organism was pathogenic for animals. The bacillus has a wide distribution in Nature, having been isolated from soil, roaches, mice and cows, as well as healthy and sick children. The lack of serologic unity between strains has also been cited as evidence against its etiologic relationship to the diseases in which it has been incriminated. On the other hand, there is evidence that Morgan's bacillus assumes, under certain conditions, a pathogenic rôle. It has been described as the cause of pyelitis, ulcerative colitis, fatal cholecystitis and fatal septicemia. In the present paper Havens and Ridgway (*J. Prev. Med.*, 1929, **3**, 159) describe a series of 13 cases which have sufficient symptoms in common to constitute a recognizable clinical picture. In all of these cases evidence exists that Morgan's bacillus was the cause of the disease. Characteristic of all were the sudden onset, usually with a chill, and the equally abrupt termination, often by crisis. The duration was fairly constant, averaging about two weeks. Nausea and vomiting often accompanied the beginning of the attack, but other gastrointestinal symptoms were absent, with the exception of a mild diarrhea in 5 of the cases. Headache and general myalgia were conspicuous symptoms in all. Fever was always present, the temperature rising sharply at the onset and falling rapidly at the termination. Usually the temperature was only moderately high and fairly constant from day to day, with rather marked morning remissions. There was no indication of concentration in any age group; no cases in young children were discovered. The condition resembles paratyphoid infection clinically, and is very similar to Brill's disease, as it occurs in the Southern United States. The abrupt onset, the duration, the general aching and the rapid convalescence are characteristic, but the absence of any rash and the negative Weil-Felix test make this diagnosis unlikely. Morgan's bacillus appears to be the etiologic agent.

Septic Sore Throat in 1928 in Massachusetts: Epidemiology.—Lombard (*J. Prev. Med.*, 1929, **3**, 81) states that there were between 925 and 975 cases and 48 known deaths in the epidemic of septic sore throat in Lee, Massachusetts, in July, 1928. The attack rate was 221 cases per 1000 inhabitants; the death rate was 9.6 per 1000 inhabitants. The epidemic was caused by the transmission, through raw milk, of hemolytic streptococci from the infected udder of a cow. The method by which the cow was infected is unknown, although some evidence

points toward a milk handler who was sick. Among the regular users of the infected milk the attack rate was greater in females than in males, but it shows no significant difference in the various age groups. The incubation period of the disease averaged two days. Over 90 per cent of the cases occurred within an interval of two weeks. Contact probably was responsible for less than 5 per cent of the total cases, but it is impossible to establish this definitely.

Postvaccination Tetanus and Its Prevention.—ARMSTRONG (*J. Am. Med. Assn.*, 1928, **90**, 738) states that epidemiologic evidence indicates that large insertions and the use of shields and dressings predispose to postvaccination tetanus in man. Shields and dressings markedly favor the development of postvaccination tetanus in monkeys and rabbits inoculated with a virus artificially contaminated with B. tetani. A proper vaccination is defined as one in which the insert is not more than $\frac{1}{8}$ inch in its greatest diameter and which is made by some method that does not remove or destroy the epidermis. Such insertions, when treated openly, have never, as far as known, been followed by postvaccination tetanus.

A Comparison of the Mortality in a New England Colonial Town with that of Modern Times.—RUSSELL and LUCIA (*Am. J. Hyg.*, 1929, **9**, 513) chose for their study the town of East Haven for the period of 1773–1822 and the New Haven of today. They found that the cumulative curves of age distribution of the population of Connecticut during the past century show a marked rise in median age—from eighteen years in the 1800–1810–1820 population to twenty-seven years in the 1920 population. In the colonial population the greatest mortality occurred among children and young adults. At the present time, emphasis is being placed on improving the conditions in the lower age groups with the result that more individuals are saved for the period of productivity. The number of deaths under five has decreased somewhat, but the greatest improvement has been between the ages of fifteen and thirty-five years. For both modern and colonial times, the lowest mortality is at the age of twelve years, it being approximately two per thousand.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL will be translated at its expense.